Chapter 16

Transabdominal Gamete Intrafallopian Transfer

J. Yovich

Introduction

Gamete intrafallopian transfer (GIFT) appeared at a timely phase in the development of assisted reproduction. Although successful in-vitro fertilisation (IVF) had been achieved 6 years before, those pioneer clinics which were subsequently established were having difficulty establishing credible and consistent live-birth rates.

Indeed, international, multicentre data to the end of 1986, when collected by independent authorities, showed that the live-birth rate per IVF procedure was less than 10% and many clinics were generating occasional pregnancies only (Yovich et al. 1989c). However those clinics which adopted the GIFT procedure rapidly achieved consistent pregnancy rates and many well-established units showed that the live-birth rate achieved in their GIFT programme was significantly higher than in the IVF programme. GIFT was therefore adopted enthusiastically as an infertility treatment procedure and indeed some clinics which could not establish a comprehensive IVF service found they could conduct GIFT procedures quite successfully.

Although GIFT was introduced as a treatment mode for unexplained infertility, it was soon being explored for all types of infertility, including male factor and sub-occlusive tubal disease – categories for which it is now clear that GIFT is unsuitable. Furthermore as IVF and other procedures such as ovarian stimulation and intrauterine insemination (IUI) programmes are becoming more effective, and cost factors are assuming an increasing significance, GIFT is experiencing a lower profile in infertility management. However a number of developments are occurring such as transcervical catheterisation of the fallopian tubes enabling ambulatory, non-general

anaesthesia procedures, and improved methods of preparing semen samples. These may lead to a re-emergence of the GIFT procedure.

The past, current and future eras in the evolution of GIFT can be categorised approximately as follows:

1984–1987 Period of enthusiastic initiation
1988–1991 Period of rationalisation
1992–1995 Period of reduced role
1996–1999 Period of rediscovery

This chapter will review the literature and available data with respect to these periods.

Period of Initiation of GIFT

From discussions it is clear that many of us, including Patrick Steptoe, had transferred retrieved oocytes to the fallopian tubes, sometimes with prepared sperm, during the 1970s and early 1980s when undertaking reconstructive tubal surgery following ovarian stimulation and course timing of the procedure (Perone 1991). However the first successful case, undertaken as a definitive procedure, was that reported by Ricardo Asch and his colleagues (Asch et al. 1984). In a patient having controlled ovarian stimulation with human menopausal gonadotrophin (hMG) and human chorionic gonadotrophin (hCG) 36 h before, they described a laparoscopic approach to both oocyte retrieval and tubal transfer with 2 oocytes transferred to each fallopian tube using a polyurethane catheter. The sperm and oocyte segments within the conveying catheter were separated by an air space. The twin pregnancy which resulted was both a real advance in infertility management; and an opening for Catholic workers keen to explore the advances of assisted reproduction.

Catholic workers had until then been restricted from exploring new reproductive technologies as the Vatican would not tolerate either the process of artificially bringing egg and sperm into contact outside the body, or the action of masturbation to collect the semen sample (or even the collection of semen by sexual intercourse into a condom unless there be no barrier to the possibility of natural conception) (Vatican 1987). Industrious Catholic workers have developed suitable GIFT protocols as modifications of the Asch model which enable Catholic clinics around the world to undertake the procedure without contravening religious tenets (Garcea et al. 1989).

Although the first successful GIFT procedure was performed using laparoscopic techniques, the next report, again by Asch and his co-workers (Asch et al. 1986), described a series of cases using both laparoscopic and minilaparotomy procedures. They generated 4 pregnancies from a series of poorly explained cases of infertility, including moderate male factor cases – 6 of the 10 cases were managed by minilaparotomy for both egg recovery and transfer. Of 4 pregnancies achieved, 2 progressed to term. Of interest Asch and his group still often perform minilaparotomy collections, whereas most other groups now use either laparoscopy for both oocyte retrieval and

Table 16.1. Randomised study comparing GIFT and IVF-ET undertaken at PIVET during 1985–86 for a range of infertility disorders. (With kind permission of International Journal of Fertility.)

	IVF-ET		GIFT	
	number	%	number	%
Unexplained	8/60	13	20/69	29
Tubal	78/550	14	21/74	28
Endometriosis III and IV	3/93	3	18/54	33[a]
Negative PCT	2/22	9	18/58	33
ASABs – semen	5/18	28	2/12	19
– female	4/20	24	0/2	–
Ovulatory disorders	2/31	6	6/30	20
Failed DI	4/23	17	13/43	30
Oligospermia	9/75	12	0/17	–
			11/49	22
Total	132/873	15	109/408	27[b]

[a] $p < 0.01$
[b] $p < 0.001$

tubal transfer; or transvaginal ultrasound-directed oocyte recovery followed by laparoscopic transfer.

The potential for GIFT to improve the chance of pregnancy for infertility failing to respond to conventional therapies was explored widely over the ensuing years. One early study over the period of 1985–1986 explored the effectiveness of GIFT in all cases previously enrolled in an IVF programme, but where patency had been demonstrated in at least one fallopian tube (Yovich and Matson 1990). A randomisation process was adopted where patients were given the opportunity to select the established method (IVF) or choose the new technique (GIFT) with its uncertain effectiveness, as only the initial report had appeared at that stage. The data are shown in Table 16.1 and indicate a significantly higher chance of pregnancy with GIFT than with conventional IVF and embryo transfer (ET).

In comparing the subcategories, GIFT was seen to be better for unexplained infertility, severe pelvic endometriosis, cases with poor sperm/mucus interaction (negative post-coital tests (PCTs) performed 8–12 h p.c.), some ovulatory disorders and failed donor insemination (DI). However it was not useful for cases in which the female partner had antispermatozoal antibodies (ASABs) or where there was any degree of male factor disorder, either oligozoospermia, asthenozoospermia or ASABs in the semen. Subsequently it was shown that a modification of the Asch protocol could achieve reasonable rates of pregnancy in moderate oligozoospermic cases if 2–5 times the standard numbers of progressively motile spermatozoa could be harvested for transfer (Matson et al. 1987a). This is in keeping with current knowledge that sperm from male factor cases have functional disorders (e.g. a reduced rate of acrosome reactivity); raising the numbers can improve the chance of fertilisation without necessarily increasing multipronuclear development. It can also be seen that subocclusive tubal infertility is also amenable to GIFT. Pregnancy outcomes were not significantly different in the series (Table 16.2) although there was a trend for fewer blighted ovum pregnancies but more ectopics among the GIFT cases.

Table 16.2. Pregnancy outcomes for comparative randomised study of IVF-ET and GIFT at PIVET during 1985–86. (With kind permission of International Journal of Fertility.)

	IVF–ET		GIFT	
	number	%	number	%
Biochemical	12	9.1	9	8.3
Blighted ovum	18	13.6	8	7.3
Miscarriage	3	2.35	6	5.5
Ectopic	9	6.8	9	8.3
Delivered >20 wks	90	68.2	77	70.6
Total	132		109	
Women's ages				
range	22–44		21–42	
mean	32.5 ± 4.5		32.7 ± 3.7	

Data from other clinics (Craft et al. 1988) (Table 16.3) including that of a multinational co-operative study (Asch 1989) (Table 16.4) were consistent showing successful fertilisation and subsequent implantation rates per oocyte transferred ranging from 8%–13%. At that time IVF units were reporting implantation rates per embryo transferred to the uterus as 4%–11% (Yovich et al. 1987a). Craft suggested a flexible approach to oocyte numbers transferred indicating that older women could have 10 or more eggs transferred with minimal risk of high-order multiple pregnancy. However a closer look at the data (Table 16.3) reveals an excessive risk of triplets which is greater when more than 4 oocytes are transferred; this persists even for older women.

An additional indication for GIFT is that of ovum donation which appeared to give very high pregnancy rates, possibly related to the younger age of the donors and their higher responsiveness to stimulation. However others preferred to stagger the treatment days for donor and recipient in order to maintain the confidentiality aspect, e.g. by a blend of GIFT and IVF techniques in the procedures of pronuclear stage tubal transfer (PROST) and tubal embryo stage transfer (TEST) (Yovich et al. 1987a).

Table 16.3. Segment of data from a large series of GIFT procedures in a single unit (Humana Wellington, London) with a flexible approach to treatment. The data compare egg numbers transferred with the age of the patient and chance of multiple pregnancy. (With kind permission of Lancet.)

Number of oocytes	Number of patients	Pregnancies	Pregnancy rate (%)	Pregnancy rate by age		Multiples 3+ (%)
				35–39 (%)	40+ (%)	
1–2	115	16	14	11	5	0
3–4	263	65	25	21	18	5
5–6	310	118	38	36	29	[a]7
7–8	243	104	43	47	24	[a]12
9–10	108	41	38	50	15	[b]15
>10	32	16	50	50	25	6
Total	1071	360	34	34	19	8

[a]2 quads and [b]1 quin in 35–39 yr age group

Table 16.4. GIFT results from a multinational co-operative study co-ordinated by R. Asch

Aetiology	Number of cases	Number of pregnancies	Pregnancy rate (%)
Unexplained infertility	796	247	31
Male	397	61	15
Endometriosis	413	132	32
Failed DI	160	66	41
Tubal/peritoneal	210	61	29
Cervical	68	19	28
Immunological	30	5	10
Premature ovarian failure	18	10	56
Total	2092	601	29

These latter procedures are preferable to GIFT as increasingly donor oocytes are fertilised and stored for a quarantine period prior to transfer.

Period of Rationalisation

From the annual reports of the Australian Institute of Health (AIH) National Perinatal Statistics Unit (NPSU) which maintains a comprehensive register of all IVF and GIFT procedures performed in Australia in concert with the Fertility Society of Australia (FSA) (Lancaster 1991), it can be seen that most of the expansion of assisted reproduction in recent years has been with GIFT (Fig. 16.1). However an overall peak for assisted reproductive procedures was reached in 1988. The 1989 data reveals that GIFT procedures resulted in a live-birth pregnancy rate more than double that of IVF-ET.

Scrutiny of the NPSU data for pregnancy outcome of GIFT procedures with respect to the infertility subcategory shows a very high ectopic pregnancy rate in cases with known tubal disease (Table 16.5). Others have previously reported excessive ectopic rates for any tubal transfer procedure in cases of suspected or known tubal disorder even where the tubes appear normal and patent (Yovich 1990). There is some reduction in the rate over the 2 years depicted and it is likely that tubal infertility will disappear completely from the list of disorders treated by GIFT in future.

Male factor cases have generally fared poorly when treated by GIFT. Even those amenable to the modified technique of inseminating higher numbers appear to have higher early pregnancy wastage (Rodriguez-Rigau et al. 1989; Yovich et al. 1989a). Currently, the preferred approach to male factor infertility is to conduct IVF with sperm motility enhancers such as pentoxifylline (Yovich et al. 1990c) and micromanipulation procedures such as subzonal insemination (SUZI) (Ng et al. 1988), partial zona dissection (PZD) (Cohen et al. 1989) or intracytoplasmic sperm injection (ICSI) (Palermo et al. 1992). Thereafter fertilised oocytes can be selected for transfer by PROST or cleaved embryos transferred by ET or TEST for which the results are significantly better (Yovich et al. 1989b).

There are variations in international trends for the adoption of GIFT over IVF. Fig. 16.2 shows comparisons of data for IVF, GIFT and frozen embryo

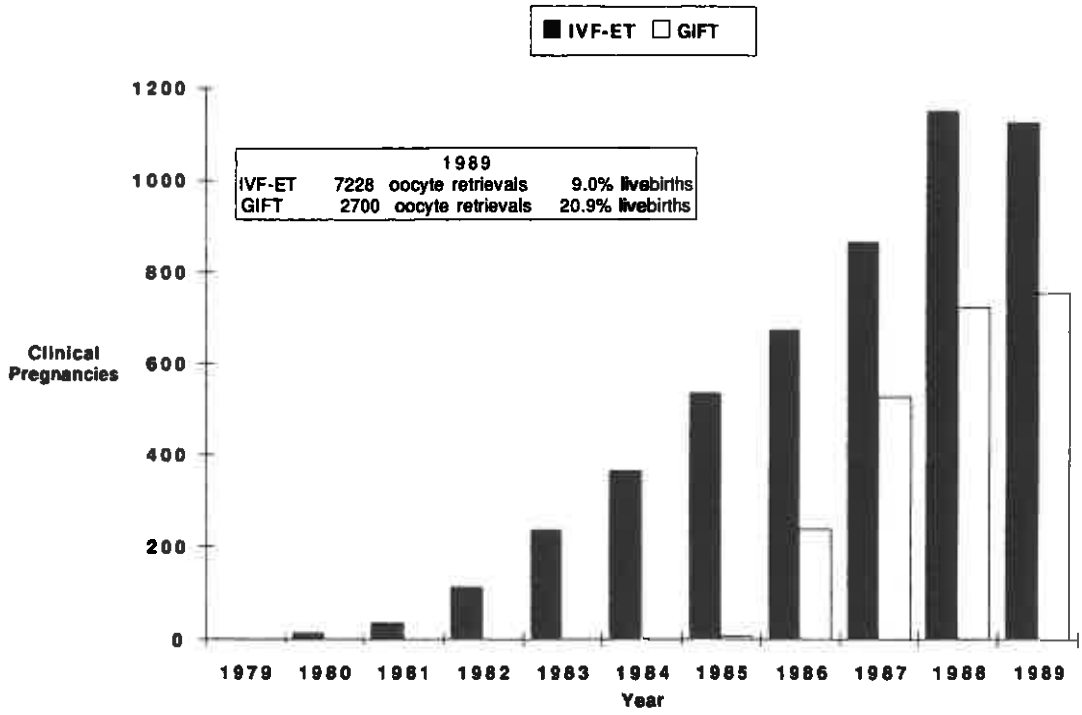

Fig. 16.1. Clinical pregnancies reported to the Australian Institute of Health National Perinatal Statistics Unit which maintains the register of cases for all assisted reproduction treatments performed in Australia and New Zealand.

Table 16.5. Ectopic pregnancy rates (%) reported from NPSU register and compared according to the main categorisation of infertility aetiology

	1988	1989
Tubal	19.1	17.9
Male	0.9	1.2
Endometriosis	4.9	4.3
Multiple	2.7	3.3
Unexplained	5.3	5.6
Total	4.8	4.6

transfer (FET) in Australia (Lancaster 1991), the United Kingdom (Donaldson 1991) and the United States (Medical Research International 1992). Of interest, Australia has a higher rate of procedures per population (1:1600 per annum) than either the UK (1:5000) or the USA (1:12 500).

Procedural Protocol

The procedure of GIFT has been modified little from that described in the original report of 1984. At PIVET the following protocol was current in 1988/89:

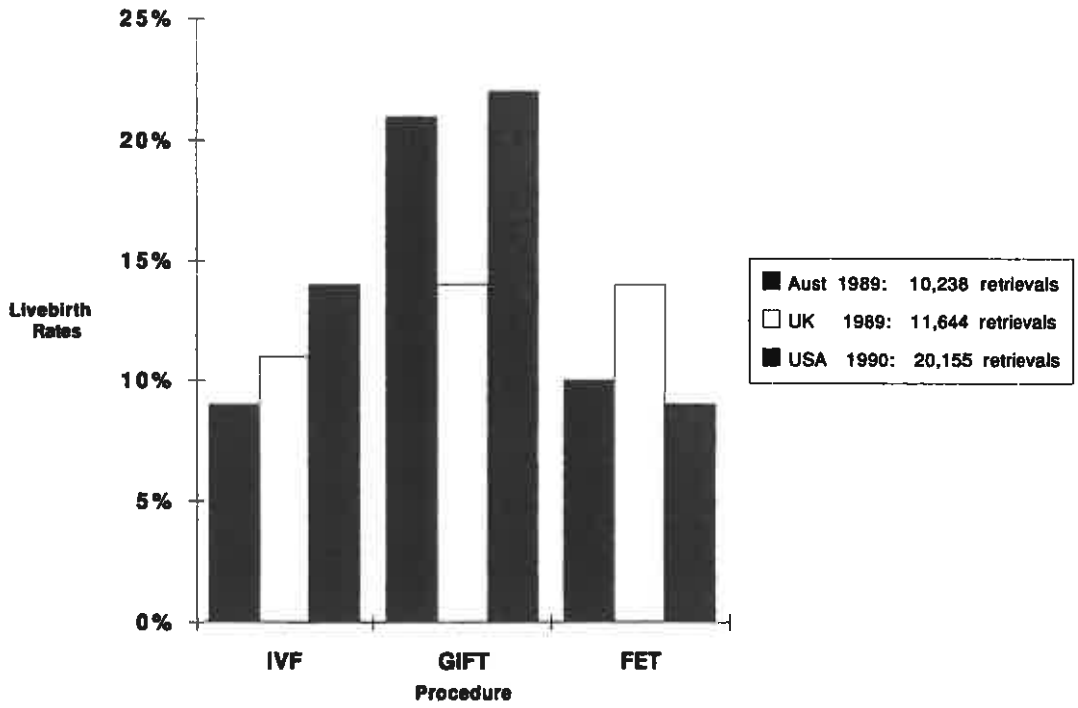

Fig. 16.2. Live-birth rates per oocyte retrieval procedure reported from the national registries of three countries. The data include the results from frozen embryo transfer (FET) procedures in addition to IVF and GIFT.

Indications:
- Where up to 4 treatments of IUI has failed for –
  - unexplained infertility
  - poor sperm/mucus interaction
  - endometriosis
  - failed DI

Ovarian stimulation
- CC/hMG
  - hCG 10 000 IU 6th day of E2 rise
- Lucrin/hMG (down regulation preferred)
  - hCG 10 000 IU 7th day of E2 rise

Oocyte recovery
- 36 h after hCG trigger
- Transvaginal ultrasonography directed recovery
- PIVET-Cook aspiration/flushing needle

Laboratory
- Semen collected 2 h before
- Oocytes graded over 4 points
- Supernumerary oocyte options
  - fertilisation and cryopreservation
  - donation to another couple or approved research
  - discard

Gamete Transfer

3 oocytes in HTFM + 20% deactivated maternal serum (dMS) in 25 μl
100 000 sperm in HTFM + 20% dMS in 25 μl
Gametes transferred to one tube at laparoscopy with Cook Teflon catheter

Luteal Phase

Proluton 50 mg imi days 0, 1, 2, 3, 4 hCG 1000 IU days 4, 7, 10, 13 where 0 is day of GIFT

Transferring all oocytes to one tube is preferred as the implantation and pregnancy rate is unaffected whilst the procedure is more rapid and tubal trauma is minimised. It appears to be of value to aspirate all peritoneal fluid prior to transfer; to insert the transfer catheter fully 4 cm into the tube; and to have the patient horizontal (rather than head-down) at the moment of transfer.

The data for assisted reproduction treatment cycles from PIVET over 1988/89 are shown in Fig. 16.3. Overall 581 couples commenced 910 treatment cycles. 172 couples completed 210 GIFT procedures with 87 diagnosed pregnant, giving a pregnancy rate per GIFT procedure of 41% per transfer; the implantation rate was 13% per oocyte transferred. 57 pregnancies proceeded to live births with 73 infants born. The live-born pregnancy rate for all treatments commenced during the period was 24.5% for GIFT (233 cycles commenced), 16.3% for IVF-ET (276 cycles commenced), 17.4% for PROST (172 treatment cycles commenced) and 14.9% for TEST (229 treatment cycles commenced). The latter two procedures contained the majority of severe male factor cases with relatively high rates of failed fertilisation, and pregnancy rates of 36% and 31%, respectively, per embryo transfer.

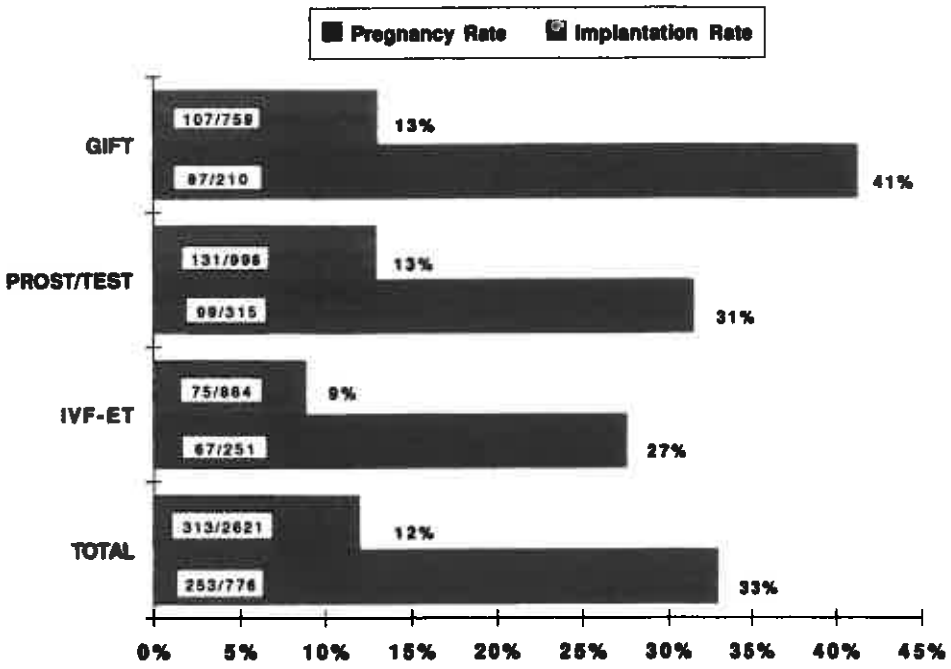

Fig. 16.3. The pregnancy rates (βhCG positive) per transfer procedure and the implantation rates (gestational sacs on ultrasound at 8 weeks per oocyte or embryo transferred) of all assisted reproduction procedures conducted at PIVET during 1988/89. The implantation rate from uterine transfer is significantly lower than from tubal transfers ($p < 0.001$).

When up to 4 oocytes were transferred the multiple pregnancy rate for GIFT was 30%, reducing to around 20% when a limit of 3 oocytes was enforced by State Government regulation. These data conform closely to the binomial model for pregnancy and multiple pregnancy rates expected (Yovich et al. 1990a). In the ensuing years there has been a slight reduction in the pregnancy rates to around 30%–33%, probably due to the blanket reduction on oocytes transferable. This effect has been shown in several prominent clinics. However there is also a trend in the data suggesting that GIFT-generated embryos have a higher implantation rate over PROST embryos which in turn have a higher rate over TEST embryos. This indicates that earlier return to the fallopian tube confers an advantage, possibly highlighting deficiencies in laboratory culture methods. All tubal transfer embryos implant at a higher rate than uterine transfers (Yovich et al. 1990a) implying one or all of the following:

1. There is a tubal factor which is beneficial to embryo growth.
2. The early post-ovulation uterine environment is hostile to embryos causing demise of all but the most robust embryos.
3. The tubal environment is physically more secure for transferred embryos.

The question of luteal support in GIFT has been extensively debated. Higher pregnancy rates than IVF can be achieved by GIFT without luteal support so generally it has not been applied. However a carefully conducted, prospective, randomised and controlled study in a GIFT series where cases were selected as least likely to require luteal support showed positive benefit (Yovich et al. 1991). The use of hCG or progesterone significantly improved the chance of pregnancy and highly significantly improved the chance of a live birth. Modelling techniques showed the effect to be greatest for poorer quality oocytes and embryos. There was an apparent benefit in combining the hCG and progesterone, particularly to minimise the need for additional early pregnancy hormonal support.

Period of Reduced Role

The world-wide activity in the field of assisted reproduction over the past decade has emphasised less invasive and less expensive treatments to generate pregnancies. The same clinics which were established to conduct IVF and GIFT procedures were able to introduce more comprehensive diagnostic facilities to investigate the underlying male and female factors.

Detailed clinical evaluation of both partners can significantly improve the chance of pregnancy in non-tubal infertility (Yovich and Grudzinskas 1990). Furthermore, some previous teachings concerning infertility management no longer hold true e.g., regarding ovarian stimulation.

Not all "normal" menstrual cycles display the hormone levels required for conception. Daily serum oestradiol (E2) indicates that peak E2 should be above 650 pmol/l at the commencement of the luteinising hormone (LH) surge and that pre-surge cervical mucus should score 6 points or more on the Insler rating. Pre-ovulatory PCTs always show a positive score (<10 progres-

sively motile sperm per high power field) when evaluated before the LH surge and when E2 levels are measured to be greater than 500 pmol/l. The PCT should be performed at least 8 h p.c. and evaluated in mucus derived from high in the cervical canal. The midluteal (7–10 days after LH surge) serum progesterone (P4) level should be greater than 30 nmol/l and E2 is usually above 500 pmol/l. The least consistent parameter in conception cycles is the size of the ovarian follicle on transabdominal or transvaginal ultrasound. In over 100 spontaneous conception cycles evaluated the average follicle diameter ranged from 14 to 27 mm when measured within 1 day of the LH surge.

Assessment cycles failing to conform to hormonal criteria are deemed Disordered Ovulatory Cycles if not frankly anovulatory. These are responsive to ovarian stimulation, either with clomiphene citrate (CC) and/or human menopausal gonadotrophins combined with hCG trigger and luteal boosts (Yovich et al. 1987b). CC cycles require careful tracking as up to 22% will display cervical mucus inhibition which will necessitate discontinuation of CC (Matson and Yovich 1987b). Cycles with raised basal LH levels (>10 IU/l) and hyperandrogenism should also avoid CC. Pure FSH is then preferred for ovarian stimulation and down regulation with a gonadotrophin releasing hormone analogue (GnRHa) may also be required. Pregnancy rates average 20% per treatment cycle and the risk of multiple pregnancy can be held below 5% by keeping peak E2 levels below 3500 pmol/l.

Where the PCT is negative, even after ovarian stimulation, intrauterine insemination (IUI) of precapacitated sperm can be effective (Yovich and Matson 1988). The insemination of 0.5 ml of culture medium containing 5–10×10^6 high-grade motile sperm 38–42 h after the hCG trigger in stimulated cycles can yield pregnancy rates of 15%–25% per treatment cycle in suitable categories. These are cases of unexplained negative PCTs, mild oligospermia, semen ASABs and female ASABs. Cases with asthenozoospermia are not suitable and those with active underlying endometriosis fare poorly. Cases of unexplained infertility may respond to IUI but the pregnancy rates are only of the order of 10%. High pregnancy rates (around 25%) are seen in donor insemination programmes employing donor IUI exclusively or after a series of failed intracervical inseminations (Patton et al. 1992). Generally 3 or 4 straws are required to generate sufficient sperm numbers.

The samples for IUI using either husband or donor sperm can be derived by sperm swim-up, sedimentation or discontinuous Percoll filtration methods. It is advisable to use whichever method will provide the cleanest possible sample as well as the highest number of highly motile spermatozoa. For asthenozoospermic cases, sperm motility enhancement can be used e.g. with pentoxifylline.

Where couples are considered to have a relatively poor prognosis in IUI, they may still wish to persist with it as a less invasive and cheaper form of treatment. The chance of pregnancy can be improved by 2 inseminations, adding a second the previous day around 18 h post-hCG (Silverberg et al. 1992). Pregnancy rates of the order of 50% can be achieved.

A comparative study between GIFT and ovarian stimulation, with or without IUI, shows a significant benefit and overall cost-effectiveness for GIFT (Table 16.6) (Wessels et al. 1992). However, high pregnancy rates

Table 16.6. Comparative pregnancy rates (%) per treatment cycle for GIFT or ovarian stimulation with or without intrauterine insemination. Asterisk marks infertility subgroups where GIFT was shown to be more cost-effective. (With kind permission of Fertility and Sterility.)

	GIFT (161 cycles)	Ovarian stimulation with or without intrauterine insemination (185 cycles)	
Idiopathic	23.6	36.8	
Endometriosis*	31.6	5.3	$p < 0.01$
Cervical factor*	28.6	–	
Anovulation	50.0	26.3	$p < 0.01$
Immunological*	25.0	15.8	
Multifactorial	14.3	10.5	
Total*	26.7	9.7	$p < 0.0001$

were achieved in the simpler programmes when the subcategory was unexplained infertility or ovulation disorder, indicating the need for rationalisation and individual selection. This view is enhanced by a study showing that the cumulative probability of conception for GIFT or PROST is similar regardless of whether IUI treatment cycles had been conducted beforehand (Robinson et al. 1992).

In clinical practice, patients and clinicians tend to be most comfortable (in an ethical sense) progressing through treatment options in a staged fashion, electing for the least complex, least invasive and least expensive treatment mode which confers a reasonable chance of pregnancy. For some patients age and distance factors may predicate towards GIFT or IVF as an early option but for the majority, GIFT is an early option only in cases of pelvic endometriosis and those with cervical disorders (e.g. post-laser ablation or cone biopsy). Most other non-tubal cases will prefer a trial of ovarian stimulation with or without IUI in the first instance. Cases of male factor infertility and female ASABs will prefer to be treated by IVF then PROST or TEST.

The Future: Rediscovering GIFT

The advantages of GIFT relate to its high degree of effectiveness; its single event treatment procedure (egg collection and gamete transfer); its close approximation to natural fertilisation; and the double benefit of possible fertilisation with cryopreservation of the supernumerary oocytes.

The disadvantages of GIFT are its ineffectiveness in certain types of infertility; the need to be absolutely certain about normality of the fallopian tubes; the need for complex anaesthesia; the need for high-order operative facilities and skills; and the need for a reasonably sophisticated laboratory to prepare the gametes and deal with the supernumerary oocytes.

These disadvantages are not insurmountable and there are already developments which may swing the pendulum back towards GIFT. These are given below.

Ineffectiveness in Certain Types of Infertility

Improved diagnostic procedures in male factor cases, e.g. the acrosome reaction to ionophore challenge (ARIC) test (Cummins et al. 1991); hyperactivation determined by computer-assisted semen analysis (CASA) (Burkman 1990); and the detection of reactive oxygen species (ROS) in semen (Aitken 1989), permit improved sperm preparations for assisted reproduction. Pentoxifylline and 2-deoxyadenosine appear not only to stimulate sperm motility, but also suppress ROS and improve the acrosome reactivity of defective specimens. At PIVET a number of pregnancies have now been achieved by IUI and GIFT where such sperm preparations have been performed following favourable laboratory results on the ARIC test and CASA.

Where ASABs are present in semen, improved techniques have been reported for their removal; this could also lead to improved results for GIFT (Grundy et al. 1992). However it is difficult to envisage overcoming the barrier for circulating female ASABs except by binding sperm to oocyte or by preliminary sperm microinjection prior to transfer.

Normality of Fallopian Tubes

It is good practice to evaluate all aspects of the female genital tract in the investigation of infertility. Ideally this will include a hysteroscopy and laparoscopy. Any case with a tubal disorder should not have GIFT except in the presence of minimal or unilateral disease. However, given the financial costs of such an exercise patients may prefer to bypass the investigation and rely on out-patient hysterosalpingography or defer to IVF-ET as the less complex option. Out-patient hysteroscopy and falloposcopy (Kerin et al. 1990) procedures are evolving and should make routine investigations more readily acceptable and probably more clinically relevant.

Complex Anaesthesia

Laparotomy and laparoscopy both require general anaesthesia. This usually includes neuromuscular paralysing drugs as well as intubation for effective airway control. The use of propofol as the inducing agent and the newer laryngeal airways which obviate the need for endotracheal intubation, have improved the acceptability of general anaesthesia. Cases are now conducted on a day-care basis but this is still far short of the ambulatory theatre arrangement which is suitable for IVF-ET.

Operation Facilities

The laparoscopy and minilaparotomy techniques also constitute a limitation to the appeal of GIFT from the informed patient's perspective. The development of transcervical cannulation techniques without general anaesthesia will help to expand the potential of GIFT. "Blind" cannulations, with or without ultrasound assistance, have not been satisfactory. Indeed, they may be quite difficult, thereby compromising the outcome of the treatment cycle

(Yovich et al. 1990b). Hysteroscopic or falloposcopic cannulations may prove more satisfactory but few cases have been performed to date.

Laboratory Facilities

The handling of gametes for GIFT requires the same degree of sophistication as that for IVF. In particular oocytes should not be allowed to undergo cooling which can cause irreversible damage, and gamete handling within culture solutions should enable strict control over pH and osmolality. The actual GIFT procedure can be performed with basic laboratory facilities, even mobile facilities. However, the effectiveness is often compromised and there are major limitations to the handling of supernumerary oocytes, when compared to GIFT procedures performed adjacent to a conventional IVF embryology laboratory (Matson and Yovich 1987b).

Supernumerary Oocytes

The fate of the supernumerary oocytes arising from GIFT poses technical and ethical questions. Fertilisation of supernumerary oocytes as a diagnostic guide in the GIFT procedure is only useful if fertilisation occurs. Various reports have confirmed the first observation that the presence or absence of fertilisation in the supernumerary oocytes has no predictive value for either pregnancy or failure of the GIFT procedure in that cycle (Matson et al. 1987b). The fertilisation rate of supernumerary oocytes is less than 50% (Yovich et al. 1989a), as opposed to 75% in normospermic IVF cases, which indicates that the current selection criteria for oocytes to be transferred at GIFT are appropriate.

Many workers in assisted reproduction programmes have expressed disquiet at the process of simply discarding healthy oocytes and believe that facilities should be available to offer fertilisation with subsequent cryopreservation of the pronuclear oocytes or resulting embryos for the couple's subsequent use. Alternatively the woman should be able to donate her oocytes to another couple or an approved research programme. Some GIFT clinics do not have such laboratory support facilities but at least one group has learnt to function successfully as a satellite of a "mother" IVF unit. Gametes are transferred by intravaginal culture tube (Ranoux et al. 1988) or portable incubator.

Other units, e.g. Catholic centres, may restrict oocyte numbers collected to match those which will be transferred. This may cause a dilemma when overstimulation results in the potential for additional oocytes to be released spontaneously. The simple puncture of additional follicles may reduce the risk of high-order multiple pregnancies in that situation.

Conclusion

GIFT is the most effective treatment for a range of infertility disorders but is not commonly applied as the first treatment. Following its initial enthusiastic

introduction the pendulum has tended to swing away from GIFT in many situations.

For the moment GIFT will probably remain as the preferred treatment for non-tubal, non-male factor infertility if there are no detectable ASABs in the female circulation, and if ovarian stimulation with or without IUI treatment has been tried without success. Highly successful IVF units (i.e. with overall pregnancy rates consistently above 20%) may often not consider GIFT except for cases of severe endometriosis or recurrent IVF failures in which embryo quality is consistently poor. There may be special advantages for GIFT in those situations. Sometimes GIFT will also be preferred as a treatment option where the patient's age, time considerations, geographical dislocation and convenience factors may dictate particular needs.

The future should see GIFT results improve for male factor disorders, particularly with better definition of sperm disorders and better semen preparations e.g. using pentoxifylline or 2-deoxyadenosine enhancement. However the main barriers to the utilisation of GIFT relate to the need for high-grade operating facilities and skills, and the concomitant need for complex anaesthesia. Major benefits will apply in favour of GIFT should effective out-patient transcervical procedures become established.

References

Aitken RJ (1989) The role of free oxygen radicals and sperm function. Int J Androl 12:95–97

Asch RH (1989) GIFT: Indications, results, problems and perspectives. In: Capitanio GL, Asch RH, De Cecco L, Croce S (eds) GIFT: From basics to clinics. Raven Press, New York, pp 209–228

Asch RH et al. (1984) Pregnancy following translaparoscopic gamete intrafallopian transfer (GIFT). Lancet 2:1034

Asch RH et al. (1986) Preliminary experiences with gamete intrafallopian transfer (GIFT). Fertil Steril 45:366–371

Burkman LJ (1990) Hyperactivated motility of human spermatozoa during in vitro capacitation and implications for fertility. In: Gagnon C (ed) Controls of sperm motility: biological and clinical aspects. CRC Press, Boca Raton, pp 303–329

Cohen J et al. (1989) Partial zona dissection of human oocytes when failure of zona pellucida penetration is anticipated. Hum Reprod 4:435–442

Craft I et al. (1988) Analysis of 1071 GIFT procedures – the case for a flexible approach to treatment. Lancet 1:1094–1098

Cummins JM et al. (1991) A test of the human sperm acrosome reaction following ionophore challenge (ARIC): relationship to fertility and other seminal parameters. J Androl 12:98–103

Donaldson M (1991) The sixth report of the Interim Licencing Authority for human in-vitro fertilisation and embryology (6). Interim Licencing Authority.

Garcea N et al. (1989) Is the GIFT a possibility for Catholics in the Assisted Reproduction field? Raven Press, New York, pp 313–319

Grundy CE et al. (1992) Establishment of pregnancy after removal of sperm antibodies in vitro. BMJ 304:292–293

Kerin J et al. (1990) Falloposcopy: a microendoscopic technique for visual exploration of the human fallopian tube from the uterotubal ostium to the fimbria using a transvaginal approach. Fertil Steril 54:390–400

Lancaster P (1991) Assisted Conception Australia and New Zealand 1989 (ISSN 1030–4711). AIH National Perinatal Statistics Unit

Matson PL, Yovich JL (1987a). Changes in cervical mucus following ovarian stimulation for in vitro fertilization. Infertility 10:267–277

Matson PL, Yovich JL (1987b) Gamete intrafallopian transfer in a non-IVF unit. Lancet 1:111–112
Matson PL et al. (1987a) The role of gamete intrafallopian transfer (GIFT) in the treatment of oligospermic infertility. Fertil Steril 48:608–612
Matson PL et al. (1987b) The in vitro fertilization of supernumerary oocytes in a gamete intrafallopian transfer (GIFT) program. Fertil Steril 47:802–806
Medical Research International and The American Fertility Society Special Interest Group, (1992) In vitro fertilization-embryo transfer (IVF-ET) in the United States: 1990 results from the IVF-ET registry. Fertil Steril 57:15–24
Ng SC et al (1988) Pregnancy after transfer of sperm under zona. Lancet 2:790
Palermo G et al. (1992) Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. Lancet 340:17–19
Patton PE et al. (1992) Intrauterine insemination outperforms intracervical insemination in a randomised controlled study with frozen, donor semen. Fertil Steril 57:559–564
Perone N (1991) Gamete intrafallopian transfer (GIFT): historic perspective. J In Vitro Fert Embryo Transfer 8:1–4
Ranoux C et al. (1988) A new in vitro fertilization technique. Fertil Steril 49:654–657
Robinson D, Syrop CH, Hammitt DG (1992) After superovulation-intrauterine insemination fails: the prognosis for treatment by gamete intrafallopian transfer/pronuclear stage transfer. Fertil Steril 57:606–612
Rodriguez-Rigau LJ et al. (1989) Relationships between the results of sperm analysis and GIFT. J Androl 10:139–144
Silverberg KM et al. (1992) A prospective randomised trial comparing two different intrauterine insemination regimens in controlled ovarian stimulation cycles. Fertil Steril 57:357–361
Vatican (1987) Instruction on respect for human life in its origin and on the dignity of procreation. Congregation for the Doctrine of the Faith
Wessels PH et al. (1992) Cost-effectiveness of gamete intrafallopian transfer in comparison with induction of ovulation with gonadotrophins in the treatment of infertility: a clinical trial. Fertil Steril 57:163–167
Yovich JL (1990) Tubal transfers: PROST & TEST. In: Asch RH, Balmaceda JP, Johnston I (eds) Gamete physiology. Serono Symposia USA, Norwell, USA, pp 305–317
Yovich JL, Grudzinskas JG (1990) The management of infertility: a practical guide to gamete handling procedures. Heinemann, London
Yovich JL, Matson PL (1988) The treatment of infertility by the high intrauterine insemination of husband's washed spermatozoa. Hum Reprod 3:939–943
Yovich JL, Matson PL (1990) The influence of infertility aetiology on the outcome of in vitro fertilization (IVF) and gamete intrafallopian transfer (GIFT) treatments. Int J Fertil 35:26–33
Yovich JL et al. (1987a) Pregnancies following pronuclear stage tubal transfer. Fertil Steril 48:851–857
Yovich JL et al. (1987b) Ovarian stimulation for disordered ovulatory cycles. Asia-Oceania J Obstet Gynaecol 13:457–463
Yovich JL et al. (1989a) The usefulness of simultaneous IVF and GIFT in predicting fertilization and pregnacy. In: Capitanio GL, Asch RH, De Cecco L, Croce S (eds) GIFT: from basics to clinics. Raven Press, New York, pp 321–332
Yovich JL et al. (1989b) Dyspermiae and GIFT of PROST & TEST. In: Capitanio GL, Asch RH, De Cecco L, Croce S (eds) GIFT: from basics to clinics. Raven Press, New York, pp 411–424
Yovich JL et al. (1989c) In-vitro fertilization today. Lancet 2:688–689
Yovich JL et al. (1990a) The benefits of tubal transfer procedures. In: Mashiach S, Ben-Rafael Z, Laufer N, Schenker JG (eds) Advances in assisted reproductive technologies. Plenum Press, New York, pp 271–285
Yovich JL et al. (1990b) Transcervical tubal embryo-stage transfer (TC-TEST). J In Vitro Fert Embryo Transf 7:137–140
Yovich JM et al. (1990c) Influence of pentoxifylline in severe male factor infertility. Fertil Steril 53:715–722
Yovich JL, Edirisinghe WR, Cummins JM (1991) Evaluation of luteal support therapy in a randomized controlled study within a GIFT program. Fertil Steril 55:131–139