MEDICAL PRACTICE

Clinical Topics

In vitro fertilisation in a small unit in the NHS

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Abstract

In vitro fertilisation is one of the most effective new treatments for infertility, but financial restrictions have made it impossible for it to be widely carried out in the National Health Service. We report on the establishment of a small, largely self funded, unit that was set up with the help of the local health service management. All cycles are programmed so that most work is carried out during the working week; oocyte recoveries are performed as outpatient procedures without general anaesthesia and guided by ultrasound. Roughly a tenth of treatment cycles and roughly a fifth of embryo transfers resulted in a clinical pregnancy.

Introduction

In vitro fertilisation is an established procedure in which much is now sufficiently routine to allow a standardised approach in

small unit centres. Until recently in vitro fertilisation was based on personalised follicular stimulation with intensive individual monitoring followed by laparoscopic oocyte recovery under general anaesthesia; each entails a large investment of time, money, and other resources. The growth of in vitro fertilisation has coincided with the realisation that the resources available for health care are limited, thus restricting new developments. Few health authorities anywhere fund such services. This is not entirely related to the novelty of the technique, as one survey has suggested that in Britain most fertility services are poorly funded by the National Health Service.¹ Private health insurance organisations restrict cover for infertility treatments.

Most centres for in vitro fertilisation have been established as large units with a large capital investment. Relatively small units which consume few resources exist, but they generally achieve lower pregnancy rates. The progress in and experience of in vitro fertilisation have led to a greater understanding of the physiology of ovarian stimulation and have made monitoring and oocyte retrieval less costly. In Oxford a small in vitro fertilisation service is running successfully and the intention is to exploit these advances to produce an effective programme within the constraints of limited means. It has been licensed by the Voluntary Licensing Authority.

The Oxford in vitro fertilisation programme has been developed over the past three years. All drugs, consumables, and some staff salaries are funded by the couples who are treated. Providing this service has had little or no effect on NHS revenue or capital budgets, but it could not have grown without the help of the administration and infrastructure of the NHS. Similar services can be established elsewhere along these lines, and our experience may help others who are planning them.

Establishing the Oxford unit

An in vitro fertilisation programme requires premises, capital equipment, staff, and consumables. Premises need not be large; our

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unit uses two rooms—formerly a four bedded maternity ward with adjacent nursery that serves as an embryology laboratory. The staff initially consisted of an embryologist and two clinicians. More joined as the programme expanded. Dedicated equipment was donated by charitable trusts, and other basic items are shared with hospital and university departments. The approximate cost of the laboratory equipment was £15 000. An ultrasonic scanner became available as part of an upgrading of hospital ultrasound facilities by the regional health authority. Such a machine would cost £25 000 new or can be leased for about £1200 a month. The small initial cost of drugs for the starting phase was borne by the NHS and the consumables by research grants.

Development of the programme

The programme began in January 1985 and ran seven days a week, with a small throughput of patients. Ovarian stimulation was monitored by ultrasonic scanning. Because of the difficulty of interpreting ovarian response to stimulation using only ultrasonic criteria we began measuring oestradiol and progesterone daily in the unit and meeting daily to discuss the progress of patients. The three pregnancies that resulted from the early work partially validated this approach, but the overall pregnancy rate was low and the small staff exhausted. The cycle of increasing workload leading to poorer results is familiar and documented by management trainers.² The need to rearrange the length of the working week led us to adopt a radical new approach to cycle management.³ Cycles are now managed by menstrual postponement followed by a fixed protocol of stimulation. This restricts the working week to five days with only one to two hours of ovarian scanning by one person on Saturday and Sunday.

Current practice

Since 1 November 1986 these developments have led to the following practices. Couples are referred by local general practitioners and consultants and by those further afield, by other fertility units, and by the Oxford fertility clinic. Couples are first sent a booklet outlining some basic reproductive physiology, a description of the way this unit functions, and the charges. They are also invited to an evening meeting with 20 other couples for an illustrated talk about in vitro fertilisation and a discussion about the ethics of it. Couples also meet members of the team and representatives of the patient support group, the Friends of IVF. (M Wiley, H O'Reilly, presented at annual congress of the European Society for Human Reproduction and Embryology, June 1987.) Afterwards appointments are made for a personal review, which includes a detailed analysis of semen. Screening for rubella and hepatitis antibodies is arranged through the referring doctor.

In the cycle before starting treatment menstruation is delayed with oral norethisterone 20 mg daily from the mid-luteal phase of the cycle. Oral clomiphene 100 mg daily for five days is then started, followed by three intramuscular doses of 225 units of human menopausal gonadotrophins every second day until two days before oocyte recovery, which is timed 35 hours after an injection of human chorionic gonadotrophin. Recovery is performed using a modification of the technique of Lenz *et al*⁴ for percutaneous transvesical ultrasound guided oocyte recovery with a double needle system,⁵ with intravenous diazepam (up to 10 mg) and pethidine (up to 100 mg) for sedation.

Laboratory procedures for gamete and embryo handling are modified from standard procedures.^{6,7} Inseminations are almost invariably carried out between 5.5 and 6.5 hours after oocyte recovery⁸ rather than timed according to maturation of accessory cells. This means that laboratory work is almost always completed in a normal working day. Embryos are transferred usually by the research nursing sister, using a transcervical catheter two days after oocyte recovery.

Support

In vitro fertilisation is stressful, and support comes from regular contact with members of the unit and where necessary from hospital medical social workers. The couples have founded a charity, the Friends of IVF (M Wiley, H O'Reilly), a self help group which also raises funds for the unit. Couples who are having treatment are kept well informed by a newsletter produced regularly by the Friends of IVF. Support and information are not only important for the couples in reducing stress but also help to ensure compliance with the complicated procedures required for in vitro fertilisation.

Financial administration

The money needed to run this service was provided by an imaginative response from the local health service management. Most NHS centres in Britain that offer artificial insemination with donor semen (AID) ask couples to pay the exceptional costs.¹ Under the Department of Health's regulations patients cannot be charged for treatment in NHS institutions unless they are private patients, and so couples who enter the in vitro fertilisation programme in Oxford are treated as if they are private patients, although medical staff provide their services free. All consultations and investigations before and after in vitro fertilisation are considered normal NHS treatment, but because this is a private service the NHS authorities are able to charge for the use of their facilities. The money that is raised covers the costs of drugs, all consumables, the salaries of a nursing sister and 1.5 members of scientific staff, rent of and services to the clinical room, and administrative overheads.

When the service began each couple paid £210 for each treatment cycle irrespective of outcome. This now costs £400, but the increased success rates for oocyte recovery and fertilisation have made it possible to offer rebates of £200 where an oocyte recovery is cancelled and £100 should a recovery be attempted and no oocytes collected.

During the whole of the current phase of this programme, 105 treatment cycles that were started have resulted in 12 clinical pregnancies, in addition to some "biochemical pregnancies" which failed to reach 6 weeks' menstrual age. The table gives the figures.

Clinical results for in vitro fertilisation programme, current phase, 1 November 1986 to 30 April 1987

No of cycles treated	105
No of oocyte recoveries	98
No of successful oocyte recoveries	86
No of embryo transfers	65
No of clinical pregnancies	12
Embryo transfer rate per successful recovery (%)	76
Clinical pregnancy rate per successful recovery (%)	14
Clinical pregnancy rate per embryo transfer (%)	18.5

Discussion

While overall numbers are still relatively small, which is inevitable in a small unit, the success rate in the current phase of the Oxford programme is comparable to most larger in vitro fertilisation centres. About one quarter of all treatment cycles fail to proceed to successful oocyte recovery, but of those that do one couple in 10 can expect a clinical pregnancy.

The protocol developed in Oxford has evolved as experience has been gained and differs from others in several important ways. The use of programmed cycles means all scientific and most clinical work is done during normal working hours, with a short session on each day of the weekend for ultrasonic scanning to review follicular development. Scheduling oocyte recovery several weeks in advance enables staff to plan holidays and other absences and couples to plan their visits to the unit. Time is the scarcest resource in any health service.² The absence of routine work at weekends has reduced the overtime bill for nursing and scientific staff.

Programming cycles also allows a successful programme to run with reduced monitoring of follicular development. Assay of steroid hormones is still important, but the information is used retrospectively rather than as a prospective guide.

Outpatient oocyte recovery under the control of ultrasound enables a unit that has no facilities for laparoscopy to offer in vitro fertilisation. Having an IVF programme in an academic department that studies the development of early pregnancy provides the opportunity for clinical research as well as a treatment for fertility problems.

There are other costs to the NHS that do not appear in our budget. Although we follow the Voluntary Licensing Authority guidelines and transfer only a maximum of three embryos to the uterus, just under a third of the current pregnancies are twins, and although we have had no neonatal problems yet, this form of fertility treatment may have clinical consequences for neonatal units.

The most successful units in the world are usually those that devote large resources to in vitro fertilisation. This is not practical for every unit, and couples may find travelling to prestigious units and living away from home stressful and expensive. Adopting new approaches tailored to the needs of small units means that in vitro fertilisation can be successful and need not be a burden on NHS resources.

This project would not have succeeded without the help of Professor Alec Turnbull, Nuffield Professor of Obstetrics and Gynaecology. It could not

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New Drugs

Adverse reactions. I

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"At the beginning of the twentieth century syphilis was the great mimic of systemic disorders. Later, tuberculosis took over this role. Both of these diseases have been tamed by chemotherapy and now 'drugs' head the list of disease simulators."

Committee on Safety of Medicines, 1985¹

Adverse drug reactions are a great concern of the general public, the pharmaceutical industry, the regulatory authorities, and the professions. It is only recently, however, that the concept that the use of drugs carries a variable but finite risk has become widely accepted. The evaluation of this risk and its relation to the benefits of treatment determine not only whether a drug is developed and licensed but also how widely it will be used. An understanding of the ways in which drug safety is assessed is therefore important in understanding the available information and assessing the risk to

individual patients. This paper reviews the current methods of monitoring adverse reactions and how they have contributed to detecting drug toxicity in recent years.

Classifying adverse reactions

Though several classifications of adverse reactions have been proposed, most are too complex for routine use. The suggestion by Rawlins and Thompson that adverse reactions can be divided into only two categories² is therefore welcome and provides a pragmatic basis for understanding drug toxicity.

Adverse reactions may present as an augmented but qualitatively normal response to a drug (type A) or as a bizarre, unexpected response (type B). Type A reactions occur in patients who are unusually susceptible to the pharmacological action of the drug—examples include postural hypotension with antihypertensive agents, gynaecomastia with dopamine antagonists, and diarrhoea with broad spectrum antibiotics. These reactions are fairly common, are increasingly frequent at higher doses, and can be predicted from a knowledge of the drug's actions. A reduction in dose will improve the symptoms, which are not usually severe and seldom cause death.

By contrast, type B reactions are usually severe and proportionately more often fatal. They are not related to the drug's known pharmacological effects and do not improve when the dose is

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