

## Contemporary Themes

# Clinical implications of developments in in vitro fertilisation

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### Abstract

During February 1979 to December 1983, 831 infertile couples were treated by in vitro fertilisation and embryo transfer. The problems they faced included deciding on the number of oocytes to be collected at laparoscopy, the numbers to be donated or fertilised, the numbers of embryos to be transferred and frozen, and whether abnormal embryos should be used for research or discarded.

The 831 patients received a total of 1530 treatment cycles. Of the 763 patients for whom complete data were available, 136 (17.8%) became pregnant. The rate of pregnancy, however, increased dramatically from 7.4% when only one embryo was transferred to 21.1% and 28.1% when two and three embryos were transferred, respectively. The chance of multiple pregnancy also increased with the number of embryos transferred, but the risk (2% for twins) was far outweighed by the relatively poor result after transferring a single embryo. Out of 40 embryos freeze-thawed, 23 survived thawing and were transferred; of these, 4 (17%) resulted in pregnancy. Thirty four transfers of donor oocyte embryos also resulted in four pregnancies (12%), but two of these ended in abortion.

Neither microscopy nor any other available test can determine the potential of an oocyte to result in pregnancy, so that discarding oocytes that may look abnormal simply reduces the chances of conception—both for the patient and for any prospective recipient of donor oocyte embryos. In any case, abnormal embryos tend to die when growth is allowed to continue in vitro. Probably all oocytes harvested from a patient should be inseminated and the utilisation of the embryos decided once the number developed is known.

### Introduction

New developments within the in vitro fertilisation programme, the increased incidence of multiple pregnancy, freeze-thawing of embryos,<sup>1</sup> and oocyte donation from one woman to another<sup>2</sup> have increased the decisions facing infertile couples during treatment. Hence up to date information is required which

doctors and patients may consider when making such decisions. The rapid introduction of new techniques and improvement in results make conclusions based on past experience uncertain, so that decisions need to be constantly reviewed as new data become available.

Decisions facing the couple may include the number of oocytes to be collected, the number of oocytes to be donated to another woman, the number of oocytes to be fertilised, the number of embryos to be transferred to the uterus, the number of embryos to be frozen, and whether abnormal embryos are to be used for research or discarded. Many of these issues are interrelated, so that to make an informed decision the couple need to understand the various steps and likely outcome of in vitro fertilisation, embryo transfer, freeze-thawing, and donation of oocytes.

We present the results of 1530 treatments and discuss some of the issues.

### Methods

The procedure for in vitro fertilisation<sup>3,4</sup> includes stimulating the ovaries to produce multiple development of follicles and collecting oocytes by laparoscopy under general anaesthesia. The data presented here were selected as the most appropriate on which decisions about current management can be based, taking into account the evolution of techniques, the improvement in success rates, and the need for a large enough sample. In components of management developing rapidly only recent data were used, whereas in analyses requiring large numbers data are presented for the whole period of the study—that is, from February 1979 to 31 December 1983. During that time 831 couples received 1530 treatments.

The most predominant groups of patients in the study were those with both tubes blocked or in whom the cause of infertility was uncertain (table I). This second group included patients in whom no cause could be found, those with one tube patent, and those with minor hormonal disorders, such as occasional anovulation or mild intermittent hyperprolactinaemia. The mixed group (table I) consisted of patients mainly with tubal problems associated with some other factor, such as male infertility, endometriosis, or ovarian disease.

### Results

Rates of pregnancy (birth or histological identification of abortion) after in vitro fertilisation were not affected by the cause of infertility. Age also had no effect, though among women over 40 no pregnancies occurred in 52 treatment cycles. The small number in this age group (3% of the total sample) had little effect on overall results.

Each year during the study period the number of oocytes collected and the fertilisation rate increased. Hence we used the data for 1983 to calculate the chance of each oocyte collected forming a normal embryo. Of the 1683 oocytes collected during that year, 1291 (76%) were fertilised successfully (two pronuclei) and 1220 (72%) formed apparently normal embryos.

The chance of pregnancy increased dramatically with the number of embryos transferred, ranging from 7.4% with one embryo to 28%

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TABLE I—Causes of infertility and numbers of treatment cycles given (1979-83 data)

No (%) of treatments	Classified causes					Total	Cause not classified	Grand total
	Both tubes blocked	Uncertain*	Male factor	Endometriosis	Mixed			
	520 (36.7)	441 (31.2)	202 (14.3)	49 (3.5)	203 (14.3)	1415 (100.0)	115	1530

\*See text.

with three; the largest difference was seen between patients with one and two embryos transferred (table II).

The chance of multiple pregnancy also increased with the number of embryos transferred (table III). Analysis was restricted to 1983, when there was a noticeable rise in the incidence of multiple pregnancy. Of the 74 births in that year resulting from in vitro fertilisation and embryo transfer, 13 (17%) were of twins and four (5%) of triplets. In the future the incidence of multiple pregnancy may fall, as shortly after the study period the advised number of embryos transferred was reduced to two or three.

TABLE II—Chance of pregnancy per treatment cycle according to number of embryos transferred (1979-83 data)

	No of embryos transferred*			
	1	2	3	4
No of patients	296	223	196	48
No (%) who became pregnant	22 (7.4)	47 (21.1)	55 (28.1)	12 (25.0)

\*In 68 patients the number of embryos transferred was not certain.  
 $\chi^2_3 = 39.3$ ;  $p = 0.00005$ .

TABLE III—Chance of multiple pregnancy according to number of embryos transferred (1983 data)

No of embryos transferred	No of patients	No of births		
		Singleton	Twins	Triplets
1	90	4	1	
2	140	15	3 (2%)	
3	174	33	9 (5%)	3
4	23	5		1 } (2%)

Freeze-thawing of embryos was successful using a slow thaw technique and dimethyl sulphoxide as a cryopreservative (dimethyl sulphoxide protects cell membranes from damage during the freeze-thaw process). This resulted in four pregnancies from 40 embryos thawed. Twenty three of the 40 embryos survived thawing and were transferred, so that the four pregnancies represented a success rate of 17% among transferred thawed embryos.

Donor oocyte embryos resulted in four pregnancies from 34 transfers; two subsequently ended in abortion.

## Discussion

The much lower pregnancy rate when only one embryo was transferred (compared with two or three) was not due to a greater age of the patients. The number of embryos transferred in women over 40 did not differ significantly from that in younger women ( $\chi^2 = 5.9$ ;  $p = 0.20$ ). Edwards *et al* found higher pregnancy rates in the natural cycle in their series (16% for single embryo transfers),<sup>5</sup> which suggests that our patients given single embryo transfers after stimulation (pregnancy rate 7.4%) represented a less fertile subsample of the population treated. For example, their ovaries may not have responded well to stimulation, so that fewer oocytes were collected and fewer embryos developed and were transferred; or the quality of the oocytes may have been poor so that they failed either to fertilise or to develop into normal embryos. Adverse change in uterine receptivity after stimulation was less likely to explain the low pregnancy rate after single embryo transfer.

Of patients from whom one or two oocytes were collected at laparoscopy, almost all preferred fertilisation and immediate embryo transfer in an attempt to achieve pregnancy. The much

lower pregnancy rate after the transfer of one embryo than two embryos (7% *v* 21%) may be sufficient reason to accept the risk of twins (about 2%). Our couples more readily accepted the risk of twins because of the limited chance of conceiving repeatedly by in vitro fertilisation and embryo transfer and a reduced span of reproductive opportunity by virtue of increased age. The further improvement in chance of pregnancy (28%) when three embryos were transferred was associated with a further increase in the risk of multiple pregnancy (about 7%), including the possibility of triplets (table III).

A pronounced reduction in fertilisation rate may occur when sperm motility is less than 50% and sperm morphology is abnormal (>60% abnormal forms),<sup>6</sup> and these couples should be advised to use all oocytes for in vitro fertilisation. Insufficient information is available concerning pregnancy rates after successful in vitro fertilisation in the presence of subnormal semen to determine whether the number of embryos transferred should be different from that in other patients.

Usually more than two oocytes are collected; in 1983 the average number collected at laparoscopy was 3.25. Oocytes rarely look abnormal on microscopy, but any that do are discarded. The potential of an oocyte to result in pregnancy, however, cannot be defined by microscopical examination or any other test at present, so that discarding oocytes reduces the chances of conception. Nevertheless, if a couple wish to reduce possible embryo wastage for ethical reasons, which is rare, then in vitro fertilisation may be attempted in a natural cycle when only one oocyte is collected, or multiple oocytes may be collected after stimulation and only one fertilised.

After the study period the average number of oocytes collected at laparoscopy rose to 4.2, and 15 were donated from couples having four or more collected, a donation rate of about 30% in this group. Couples with fewer oocytes collected did not donate. The couples are told that donation may help other women conceive who have absent or inaccessible ovaries or no oocytes in the ovaries, or whose oocytes transmit genetic disease. The donors are not paid, donation is anonymous, and the recipient is matched for physical and social characteristics of the donor. A condition of oocyte donation is that the donor may be informed of the occurrence of pregnancy in the recipient. The donor is warned that she may feel resentful if the recipient becomes pregnant and she does not.

Most patients have all oocytes inseminated and decide on the utilisation of the embryos once the number developed is known. Because of the risks of multiple pregnancy, including the psychosocial and physical complications in the mother and child, couples are now advised to restrict the number of embryos transferred to two or three. Rarely, a couple insist on having four embryos transferred in the hope that this will enhance the chances of conception. Embryos in excess of two or three are frozen so that the couple may increase the chance of eventual pregnancy. The embryos are thawed and transferred as soon as possible if the first embryo transfer fails or one or more years later if a second child is wanted. After the study period the success of freeze-thawing became known to couples in the programme. Out of 111 patients having oocytes collected, 60 decided to have embryos frozen. The possibility of freeze-thawing is discussed when the patient enters the treatment cycle, and the final decision concerning the number of embryos to be freeze-thawed is made when the number of normal embryos developed is known. In practice, couples with more than two or three embryos collected have two or three transferred immediately and the remaining embryos

frozen. Because only about half the embryos survive freeze-thawing, usually all the frozen embryos are thawed together. The number of embryos freeze-thawed ranges from one to four.

Probably some couples will change their attitude to the use of frozen embryos, owing to divorce, death, or disease in one partner or changing psychosocial circumstances. At present unwanted embryos may be donated, discarded, or given for research. Our preference is for donation, which helps other infertile couples. Prenatal adoption of unwanted embryos may have advantages over postnatal adoption. Matching of donors and recipients may be more accurate, as adoption agencies are restricted by the small number of babies available and the long waiting lists in selecting adoptive parents, whereas storage of a large number of embryos (as in semen banks) will permit selection by matching donor and recipient characteristics. The recipient of the embryo experiences the emotional changes of pregnancy and birth, and the mother-child relationship may be favourably influenced by these and the early postnatal experiences.

Shortly before this report one couple died in an aeroplane accident after two embryos developed from the wife's oocytes and donor sperms had been frozen; this raised not only the problem of use of unwanted embryos but the possibility of the legal rights of inheritance of the embryos should they be transferred and survive.

We find that abnormal embryos die when growth is allowed

to continue in vitro. A high early embryonic mortality has been established in man and other species.<sup>7-9</sup> Couples do not accept abnormal embryos for transfer and prefer them to be examined in an attempt to define the type and cause of the abnormality. This knowledge increases the understanding of early embryo development, which may help other infertile couples and may be relevant to determining the causes of fetal malformation.

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## USSR Letter

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### The unmarried mother and her child

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Although the Soviet authorities publish relatively little demographic data on a regular basis, they make no secret of the substantial imbalance between the numbers of men and women in the USSR. Each annual abstract of statistics contains a time series which gives a breakdown of the population by sex (though not by age); the latest volume reports that on 1 July 1983 the population consisted of 145.0 million women and 127.5 million men. The difference was thus 17.5 million, which may be compared with the even larger figure of 20.7 million at the 1959 census.

The main cause of this disproportion between the sexes is the colossal number of male deaths in the hostilities, and in many other less publicised contexts, during the second world war. Nevertheless, there is a secondary influence to which attention should be drawn: the persisting differential in mortality rates. For the age groups 20 to 50, according to an entirely reliable source, "the mortality of men is *twice as great* as that of women" (my italics).<sup>1</sup>

#### Pronatalist propaganda

In view of the authorities' longstanding anxiety over the low birth rate in many parts of the country, it is not surprising that from an instrumental viewpoint the cohorts of younger unmarried women should be regarded as a demographic resource. A few years ago one highly placed expert, Professor Boris Urlanis, provided a vigorously expressed example of that attitude in the mass circulation newspaper *Nedelya* (*The Week*).<sup>2</sup>

Having criticised frequent recourse to abortion by married women, he turned his attention to those whose chances of finding a husband are slim, whether owing to their age, temperament, or place of work. (The last factor relates not only to specific occupations but also to whole communities because some towns are almost entirely devoted to light industry employing women.) Urlanis wrote that such a woman should understand her position and "ought to be aware also that motherhood sometimes brings more joy (or, in any event, not less) than matrimony, especially if matrimony is not accompanied by love and respect."

For Urlanis a reduction in the number of abortions among unmarried mothers represented a priority task which he perceived as simultaneously furthering the interests of the woman and her country. Implicitly, at least, he dismissed the significance of social and psychological problems entailed by having to raise a child alone. With facile chop logic he asserted: "She is not really single if she has a baby! There are two of them—they have a family!" Given that unmarried mothers received "a maximum of attention and

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