ASSISTED CONCEPTION

Health Services and Evaluation

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Abstract

Comparison of assisted conception in Australia, the United Kingdom, and the United States indicates that further rapid growth in services is likely in many countries. Better data on pregnancy rates and the outcome of pregnancy, as well as standardized reporting of national results, are needed to monitor the effectiveness of treatment.

The reproductive revolution of the 1980s has brought children to previously infertile couples, changed the demographic profile of the population, especially in regard to multiple births, and raised numerous social, moral, legal, ethical, and religious issues. When global overpopulation is considered, it seems paradoxical that significant resources are expended on providing infertility services. However, involuntary infertility often has profound effects on the lives of infertile couples (38). Although in-vitro fertilization (IVF) and related techniques are still disputed by some as a legitimate method of treating infertility (41), the continuing increase in many countries in the number of IVF units, pregnancies, and births indicates widespread acceptance by infertile couples.

This article discusses health services for treating infertility by assisted conception, and the evaluation of these services, but not the ethical and legal aspects. It gives a mainly Australian perspective, with some reference to developments in other countries, especially the United Kingdom and the United States. The comprehensive report on infertility by the Office of Technology Assessment of the Congress of the United States (38) provides a much broader review of regulatory and legal issues, both in that country and elsewhere. Artificial insemination will not be considered here.

Information about fertility patterns has been widely available for many years, but infertility as a public health issue has received little attention. There have been few population-based surveys of the prevalence of infertility. No estimates are available of the proportion of infertile couples that might benefit from treatment by assisted conception.

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In the United States in 1982, 8.5% of married couples with wives in the reproductive age group (15–44 years) were infertile, that is, they had failed to conceive after 12 months of unprotected intercourse (38). This constitutes a major public health problem, affecting an estimated 2.4 million couples. Excluding surgically sterile couples, 13.9% of the other couples were infertile.

TREATMENT OF INFERTILITY BY ASSISTED CONCEPTION

IVF and related techniques are used mainly for treating infertility due to disease and obstruction of the fallopian tubes, but they are also used when infertility is the result of male factors, endometriosis, ovulation defects, and unexplained infertility. In a relatively high proportion of couples, there are multiple causes of infertility.

Before a typical treatment cycle begins, couples are counseled about the likely outcome of treatment. After ovulation has been stimulated by various combinations of drugs, oocytes are collected either by laparoscopy or by ultrasound-guided transvaginal methods, then fertilized in the laboratory or transferred with sperm to the fallopian tubes. Cancellation of treatment occurs in about 10–20% of stimulated cycles, usually because of inadequate response to drugs or premature ovulation (20).

In IVF, the dividing embryos are replaced in the uterus about 36–48 hours after fertilization in the laboratory. In gamete intrafallopian transfer (GIFT), the gametes (oocytes and sperm) are transferred to the fallopian tube so that fertilization occurs in vivo. Occasionally, drug treatment may be used during the succeeding few weeks of the luteal phase.

These standard techniques of IVF and GIFT may be varied either by freezing embryos for use in future cycles, by donation of oocytes or sperm, or by freezing oocytes. Occasionally IVF and GIFT may be combined, as when early embryos resulting from fertilization in the laboratory are transferred to the fallopian tubes. Newer techniques of fertilization for treating infertility due to sperm abnormalities include microinjection of sperm directly into the oocyte or insemination after breaking the zona pellicula, the oocyte's outer layer (37). Other modifications of the treatment cycle have been introduced in an effort to improve the relatively low IVF pregnancy rates. Some of these new drug combinations (25) may require a longer duration of treatment but enable planning of the day of oocyte retrieval.

HEALTH SERVICES FOR ASSISTED CONCEPTION

Clinics and units for treating infertile couples by assisted conception have been established in about 50 countries, including many developing countries such as Nigeria, Indonesia, and Colombia. Initially, most IVF units were linked to academic departments of obstetrics and gynecology in teaching hospitals, but these services are now provided in other private and public hospitals. Some networks of units have been set up in several countries and may be commercially operated by infertility practitioners or by pharmaceutical companies.

In the few countries for which data are available, there continues to be an increasing trend in the number of treatment cycles and pregnancies. Figure 1 shows the increase in clinical pregnancies occurring after assisted conception in Australia and New Zealand from 1979 to 1988. A distinction is made between viable pregnancies of at least 20 weeks gestation and other early pregnancy losses. Population-based data on the number of treatment cycles were not available for most of this period. One in 200 of all births in Australia in 1988 resulted from assisted conception. Diffusion of clinical services for IVF appears to have been more rapid in Australia than in other countries. Long-
standing research in reproductive biology and IVF in Melbourne provided the impetus for developing clinical services there in the late 1970s. Regular workshops on the scientific and clinical aspects of IVF, as well as the relative geographic isolation of Melbourne from other major cities, led quickly to other units being set up in Australia, then across the Tasman Sea in New Zealand. As early as 1983, there were nine units in Australia and one in New Zealand (5).

Under the federal system of government in Australia, health services are regulated by each of eight states and territories. In some states, the number of units has been restricted by legislation; in others, the services have developed according to perceived needs, as seen by infertility practitioners and hospital administrators. No doubt in some hospitals an IVF unit is regarded as enhancing the hospital’s prestige and status.

The perceived needs for IVF services in Australia may be almost met because waiting lists for treatment have dwindled and some units choose to close for several periods of about a month each year. When there were fewer IVF units, some couples put their names on several waiting lists, thus creating an artificial demand for services.

Private hospitals have increasingly been utilized for IVF because there is a premium on the use of operating rooms in public hospitals and access may not be available at short notice. In stimulated cycles, the timing of oocyte collection cannot always be planned well in advance, so premature ovulation may sometimes occur. Ultrasound-guided transvaginal oocyte collection was introduced partly because it reduced the need for general anesthesia and operating rooms.

Not all units have laboratory facilities for freezing embryos and for treating some women by use of donor oocytes. In 1987, 15 (75%) of the 20 IVF and GIFT units in Australia and New Zealand had facilities for freezing; 9 (45%) used donor oocytes

Figure 1. Number of pregnancies resulting from assisted conception, Australia and New Zealand, 1979–88.
Among 34 approved centers in the United Kingdom in 1987, 15 (44%) used embryo freezing and 11 (32%) used donor oocytes to treat infertility (40). Of the 96 reporting clinics in the United States in the same year, 39 (41%) froze embryos and 17 (18%) used donor oocytes (26).

The regulation of assisted conception services seems to vary widely in different countries. In Australia (19) and in the United States, voluntary guidelines have been developed by professional societies that are made up of infertility specialists, scientists, nurses, and counselors working in IVF units or in the more general field of infertility. Compared with other fields of medical practice, these professional groups have been unusually active in developing standards for practice, doubtless prompted partly by public debate on numerous controversial issues regarding assisted conception. Consumer support groups have also played an important role as advocates for the needs of infertile couples.

Both the Fertility Society of Australia (10) and the American Fertility Society (1) have published standards or guidelines for the practice of IVF and related reproductive technologies. The purposes of the Australian guidelines are to ensure that:

1. Each unit is competent in the clinical and scientific aspects of assisted conception. Staff should have appropriate knowledge, skills, and experience for counseling clinical practice and laboratory work. There should also be appropriate facilities for ultrasonography, hormonal assay, collecting oocytes and transferring embryos, and general anesthesia, with laboratory facilities close to the operating area.

2. Appropriate counseling is given before treatment about the social, medical, and financial implications of IVF and is also available during and after treatment.

3. Adequate records are kept of treatment cycles and procedures, including oocyte retrieval, fertilization, cleavage, transfer, and outcome of pregnancy. Information about each unit’s results of treatment, and national data on pregnancy rates and the outcome of pregnancies, should be made available to infertile couples contemplating assisted conception.

4. Informed consent is given for procedures, ovum and embryo donation, research on embryos, and storage and disposal of embryos and gametes.

5. Research and the general work of the unit are monitored by an institutional ethics or review committee.

Review of each IVF unit’s compliance with these guidelines is conducted by the Reproductive Technology Accreditation Committee, which has rapidly achieved widespread recognition (17). Some governments, such as in the state of Victoria, have enacted legislation that provides for some of these regulatory measures and restricts the number of approved IVF units (39). A National Health Technology Advisory Panel has been established recently in Australia (14) but, with limited resources, it has not examined assisted conception. On the other hand, legal and ethical issues have been a major priority in Australia (29;34).

**How Many IVF Units Are Necessary?**

In a planned health service, decisions about the numbers of units that are needed for IVF and related services might be based on knowledge of the prevalence of infertility in the population and the proportion of infertile couples who are likely to respond to IVF and GIFT. Much of the debate about IVF has centered on social, legal, and ethical issues, but there is little indication that clinical services have been planned at the outset. For example, in the United Kingdom, only two centers are funded by the National Health Service (40).
Assisted conception

It is not known how many units for treating infertile women by assisted conception are needed in countries where such treatment is widely accepted. There are very limited data that can be used to compare IVF services in different countries, but it seems that relatively more women are treated in Australia than elsewhere.

The number of units in Australia has been determined by the perceptions of infertility specialists about needs and, in some states, by government regulation. Similar factors are probably operative elsewhere. There are now 22 units for a population of 16.7 million, or 1.3 units per million inhabitants. A similar ratio of IVF units to population has been recommended in France (74 units for a population of 55.8 million), but practitioners of assisted conception believe that this number is inadequate (9). There were, in fact, more than 100 IVF units in France in 1985 (38). The ratio appears to be lower in the United Kingdom and the United States. In the United Kingdom, there were 34 approved centers in 1987, and another 12 were setting up facilities (40) for a population of 56.8 million (0.8 per million). In the United States, the survey by the Office of Technology Assessment identified at least 169 clinics performing IVF (38) for a population of 245 million (0.7 per million).

The size of IVF units can be assessed in terms of the annual number of cycles of treatment. Varying criteria in the reports from each country preclude a detailed comparison of the actual distribution of the size of units. However, in the United States, the majority (71%) of units were small (less than 100 treatment cycles annually) (26), whereas only 3 of 20 (15%) units in Australia and New Zealand (31) and 14 of 34 (41%) units in the United Kingdom had units of this size (40). Pregnancy rates were correlated with size of unit in the United Kingdom. The live-birth pregnancy rates in the small units were one-fifth of those in the large (more than 400 treatment cycles) units. The difference in pregnancy rates between small and large units in the United States was less pronounced (26).

EVALUATION OF ASSISTED CONCEPTION

Data Systems
Population data on fertility are usually derived from birth registrations and published by national statistics organizations. Because births occurring after assisted conception are not identified in birth registrations, it has been necessary to establish separate data systems to collect information on total numbers of treatment cycles and on the outcome of pregnancies. Additional data on each cycle of treatment would assist interpretation of currently available results but would require considerable resources for collection and processing.

In 1983, the National Health and Medical Research Council in Australia and the Fertility Society of Australia requested that the National Perinatal Statistics Unit start a register to monitor the outcome of pregnancies resulting from IVF, with an emphasis on studying the risk of birth defects. Initially only data on pregnancies were collected, but in recent years information has also been obtained about the number of women treated by each IVF unit, the number of treatment cycles, and some aspects of the laboratory work related to procedures on embryos. Similar registers have now been established in some other countries but their coverage of all IVF units is not usually complete and data on the outcomes of pregnancy are often deficient. Annual reports are published in Australia and New Zealand, the United Kingdom, the United States, and France.

Most studies of the results of treatment are conducted by individual IVF units.
There have also been several international collaborative studies of assisted conception in which data summarizing treatment and outcomes of pregnancy have been collected from participating units and presented at international meetings (3;6). Other studies have attempted to determine prognostic factors that can be used to predict pregnancy rates and to counsel infertile couples (16).

In considering evaluation of the various methods of assisted conception, we should recall the successive stages of the treatment cycle. Some couples who are interviewed and counseled about the options available for treating infertility will elect not to begin treatment. Of those women who do commence a treatment cycle, decreasing numbers reach the stages of oocyte retrieval, fertilization of oocytes, embryo transfer, clinical pregnancy, and birth. Table 1 gives the Australian and New Zealand data for 1987 on the number of IVF cycles reaching successive stages of treatment, some eventually resulting in pregnancies with one or more live births. Of the cycles that were started, 12.1% did not reach the next stage of oocyte retrieval. Usually because of failed fertilization in the laboratory, a further 14% of cycles did not progress to embryo transfer. In the United Kingdom, 21.5% of cycles were canceled before oocyte retrieval; 19.9% of oocyte retrievals did not progress to embryo transfer (40). In the United States, 13.3% of oocyte retrieval cycles did not progress to embryo transfer (26).

Pregnancy Rates

Pregnancy rates provide the most important indicator of the effectiveness of assisted conception. There has been much debate and controversy about the calculation and reporting of these rates and in determining the most appropriate numerator and denominator (12;20;24;31). Although clinical pregnancies, which include spontaneous abortions and ectopic pregnancies, have been widely reported as the numerator, it is preferable to count only those pregnancies that result in one or more live births, the outcome of most significance to infertile couples (31). The rates can be expressed in terms of the number of women treated or the number of cycles of treatment. Because the average number of treatment cycles for each woman varies from unit to unit, pregnancies should be related to cycles of treatment, rather than to women, when comparing results among different IVF units. Finally, pregnancy rates can be expressed in terms of the number of cycles of treatment actually started, the number of cycles reaching the stage of oocyte retrieval, or the number of cycles in which embryos are transferred to the uterus.

The actual pregnancy rate that is used to assess whether IVF and GIFT have been successful will depend to some extent on the purpose for which the data will be used. In evaluating the costs of treatment, all women starting a treatment cycle should be included. If the IVF rates are to be compared with natural conceptions and fecundability (the monthly probability of conception), it is more appropriate to base the rates on the stage of oocyte retrieval, at which oocytes have been collected and can potentially be fertilized by sperm. Other reasons for selecting the stage of oocyte retrieval are (a) it is a significant surgical procedure for women; (b) it is not always known at the start of a treatment cycle whether IVF or GIFT will be used; and (c) it is a point between the beginning of a cycle of treatment and the stage of embryo transfer, that is, it is a compromise between the rates sought by the critics and advocates of IVF. The term “success” rate has become emotive and should not be used.

Treatment-independent pregnancies occur quite frequently among infertile couples who have not been treated or who have ceased treatment (7), including couples on waiting lists for IVF (33). The likelihood of such pregnancies varies according to the
Table 1. IVF Treatment Cycles and Pregnancy Rates, Australia and New Zealand, 1987

<table>
<thead>
<tr>
<th>Stage of treatment/pregnancy outcome</th>
<th>Numbers/rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cycles of treatment started</td>
<td>7,733</td>
</tr>
<tr>
<td>Number of cycles with oocyte retrieval</td>
<td>6,796</td>
</tr>
<tr>
<td>Number of cycles with embryo transfer</td>
<td>5,797</td>
</tr>
<tr>
<td>Clinical pregnancies</td>
<td>896</td>
</tr>
<tr>
<td>Live-birth pregnancies</td>
<td>643</td>
</tr>
<tr>
<td>Live-birth pregnancies per 100 cycles started</td>
<td>8.3</td>
</tr>
<tr>
<td>Live-birth pregnancies per 100 oocyte retrieval cycles</td>
<td>9.5</td>
</tr>
<tr>
<td>Live-birth pregnancies per 100 embryo transfer cycles</td>
<td>11.1</td>
</tr>
</tbody>
</table>


Table 2. Factors Influencing IVF and GIFT Pregnancy Rates

- Woman's characteristics
  - Age
  - Previous reproductive history
  - Cause of infertility
- Biological factors
  - Oocyte development at fertilization
  - Quality of semen
  - Embryo development at transfer
- Treatment cycle
  - Method of ovulation induction
  - Frequency of drug administration
  - Duration of treatment cycle
  - Uterine receptivity
  - Progesterone support in luteal phase
  - Number of embryos or oocytes transferred
- Laboratory procedures
  - Freezing and thawing of embryos
  - Specific cryoprotectant (chemical agent used for freezing)
  - Micromanipulation or microinjection of oocytes
  - Factors promoting growth of embryos
- Characteristics of IVF/GIFT units
  - Experience in treating infertility
  - Size of IVF/GIFT unit (number of treatment cycles per year)
- Definitions and sample size
  - Choice of numerator and denominator for calculating rates
  - Random fluctuation due to small sample size

cause of infertility. There have been no clinical trials to compare pregnancy rates in couples randomly assigned to IVF treatment and nontreatment groups.

Interpretation of IVF and GIFT pregnancy rates presents many problems analogous to interpretation of perinatal survival. Table 2 lists some of the factors that may influence pregnancy rates. Uniform definitions are required. Maternal factors such as age and previous reproductive history are important. The maturation of the oocyte at fertilization and development of the embryo at transfer can be compared to the critical influence that gestational age has on perinatal outcome. The environmental

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conditions in the laboratory, such as temperature and chemical composition of the culture medium, will determine whether embryos cleave and grow normally. Indeed, with a recent study suggesting that pregnancy rates are improved by supplementing the embryo culture (32), we are doubtless on the brink of an era of embryo intensive care. This raises ethical dilemmas similar to those in neonatal intensive care, for example, selecting which embryos should continue to be incubated and evaluating new treatment appropriately. Quality of care is less tangible but is likely to influence pregnancy rates just as it influences perinatal survival.

Pregnancy rates from individual clinics have been published extensively but should be interpreted cautiously. Even in larger IVF units, the number of cycles of treatment is usually modest. The actual rates may be influenced by policies for selecting patients according to their age (35) and cause of infertility, by reporting results for a brief optimal period of treatment, and by random fluctuations. Population-based data usually give a more realistic evaluation of pregnancy rates but need to include data from all units.

Pregnancy rates after GIFT are usually higher than those after IVF. The fallopian tube presumably provides a more suitable natural environment for fertilization and embryonic growth than does the laboratory. The clinical indications for GIFT differ from those for IVF. GIFT is not appropriate when there is bilateral tubal disease, but it has become the treatment of choice for unexplained infertility.

Fecundability (the monthly probability of conception) in the general population varies from about 20 to 40%, depending mainly on the age of the women (18). The overall live-birth pregnancy rate after IVF is about 10 per 100 cycles of treatment (Table 2), but individual women may increase their chances of achieving a live birth by increasing the number of cycles of treatment. The chance of pregnancy appears to be more or less similar in each successive cycle of treatment (21).

Reporting pregnancy rates has become increasingly complex as new techniques have been developed and some techniques have been combined. Also, when embryos are frozen and later thawed before transfer, oocyte retrieval may occur in one reporting period and embryo transfer in a subsequent period. As an example of combined treatment, a woman who is infertile because of one blocked fallopian tube may be treated by transfer of embryos to her uterus and simultaneous transfer of oocytes and sperm to her healthy fallopian tube. When donor oocytes are used, the embryos may be frozen before transfer in a subsequent cycle. As the number of pregnancies achieved by these different techniques in any single IVF unit is small, it is essential to pool data so that the overall results can be assessed. Factors that may influence pregnancy rates in the future include: (a) fewer stimulated cycles; (b) better conditions of embryo culture; (c) reduction in the number of embryos transferred, thus avoiding multiple births; and (d) modification of uterine receptivity. Lack of synchrony between the relatively slowly growing embryos and the stimulated uterine endometrium may be a factor adversely affecting pregnancy rates. Transfer of fewer embryos would also be expected to reduce pregnancy rates; however, the effect of other interventions is unpredictable.

Published reports from Australia and New Zealand, the United Kingdom, and the United States show that the pregnancy rates in individual IVF units show marked variations. It should be noted that the number of cycles of treatment in any one unit is relatively small and so there will be random fluctuations. For example, the IVF live-birth pregnancy rates in Australia and New Zealand in 1987 ranged between 2.0 and 15.0 per 100 oocyte retrieval cycles, with a national figure of 9.5 per 100 cycles (31).
Table 3. Incidence of Selected Outcomes in IVF and GIFT Pregnancies

<table>
<thead>
<tr>
<th>Outcome of pregnancy</th>
<th>IVF (%)</th>
<th>GIFT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ectopic pregnancy</strong></td>
<td>5.6</td>
<td>5.1</td>
</tr>
<tr>
<td><strong>Spontaneous abortion</strong></td>
<td>24.3</td>
<td>26.2</td>
</tr>
<tr>
<td><strong>Multiple births in viable pregnancies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Twins</td>
<td>18.9</td>
<td>18.5</td>
</tr>
<tr>
<td>Triplets</td>
<td>3.6</td>
<td>4.0</td>
</tr>
<tr>
<td>Quadruplets</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Total multiple births</td>
<td>22.7</td>
<td>22.9</td>
</tr>
<tr>
<td><strong>Low birth weight (&lt;2,500 g)</strong></td>
<td>36.1</td>
<td>34.1</td>
</tr>
<tr>
<td><strong>Cesarean birth</strong></td>
<td>44.6</td>
<td>38.4</td>
</tr>
</tbody>
</table>


Outcome of Pregnancy

Three main phases of pregnancy outcome can be considered: early reproductive loss, viable pregnancies of at least 20 weeks gestation, and the long-term health of treated women and their children.

Early reproductive loss after IVF and GIFT is higher than after natural conception. An early report showed a 5% incidence of ectopic pregnancy after IVF (4) and subsequent studies of both IVF (6) and GIFT (30) have confirmed this finding (Table 3). Because the outcome of pregnancy can be studied prospectively from the time of conception, determining the rate of spontaneous abortions in IVF and GIFT pregnancies is easier than in naturally conceived pregnancies. Nevertheless, the incidence of spontaneous abortion still seems to be high (Table 3). The abortion rate increases with advancing maternal age (30).

Multiple births are common after IVF and GIFT because more than one embryo or oocyte are usually transferred to the uterus or fallopian tubes (Table 3). Similar rates have been reported in other countries (26;40).

The data for Australia and New Zealand have consistently shown a high incidence of preterm delivery (<37 weeks gestation) in IVF pregnancies (4;5). The most recent data show an overall incidence of 26.7%; in singleton pregnancies, the incidence was 17.2% (31). Preterm birth was more common in the youngest and oldest age groups, but it was also high in the other age groups. Its incidence was highest among those couples with multiple causes of infertility, but it was higher than normal in all causal groups. Small studies from several IVF units (13;36) have not confirmed these findings, but their definitions varied. GIFT pregnancies also have a high incidence of preterm delivery (31). Factors possibly contributing to the increased risk of preterm births include the underlying causes of infertility, repeated investigation of infertile women by dilatation and curettage, and the effects of ovarian hyperstimulation (5).

Low birth weight (<2,500 g) is also more common than usual in IVF and GIFT pregnancies (Table 3). In Australia and New Zealand, the total incidence of low birth weight in IVF births was about six times higher than that in the general population. In singleton births, the incidence was 15.9%; in twins, 58.9%; and in triplets, 95.3%. In some hospitals with relatively large numbers of births and referrals after assisted conception, these infants have increased the workload of neonatal intensive care units.
The high incidence of preterm and low birth weight infants in both single and multiple births is a major factor contributing to the high perinatal mortality rates after IVF and GIFT (5). These rates are about three times higher than the comparable population figures. Recent data show that stillbirths were more than twice as common as neonatal deaths, except in multiple births after GIFT, which have a relatively high neonatal death rate (31). Some obstetric complications in previously infertile women may be associated with their relatively advanced age or the underlying cause of infertility. Few studies of obstetric complications in IVF pregnancies have been published (13). Fetal growth appears to be normal in IVF pregnancies (2;23).

The overall cesarean birth rate of 44.6% was almost three times higher than the national cesarean rate of 16.5% in Australia in 1986. In singleton IVF pregnancies, the cesarean birth rate was 39.2%; in twin pregnancies, 58.3%; and in triplet pregnancies, 81.7% (31). After GIFT, cesarean rates were lower (31.5%) than the rates for IVF in singleton pregnancies, but were similar to those for IVF in multiple pregnancies.

There have been few systematic studies of congenital malformations after IVF. In Australia and New Zealand, the total incidence of major malformations and chromosomal abnormalities detected either by prenatal diagnosis or at birth was not increased (22). There was an increased risk of spina bifida and transposition of the great arteries after IVF. Preliminary data on a larger number of IVF and GIFT fetuses and infants show a high incidence of several other malformations, especially those of the urinary tract (31). Other estimates of the incidence of malformations are based on either small samples (27) or pooled data that did not examine specific malformation rates (6).

**Follow-up Studies**

In view of the concern about the possible adverse affects of IVF procedures on subsequent survival and development, it is surprising how few studies have been published. Most of these studies were from single IVF units and lacked a suitable control group. None of them had an adequate sample size to take account of the increased incidence of multiple births and the possible adverse outcomes related to this factor.

From these limited studies, IVF has not been shown to cause specific adverse effects. One study compared 83 IVF children and 93 children who were born after natural conception, and matched by age, multiple birth, sex, race, maternal age, and socioeconomic factors (27). The children were assessed between 12 and 30 months of age. There was no evidence of developmental delay. Two other small studies without comparison groups did not indicate any adverse effects of IVF (28;44).

These studies have examined physical and developmental outcomes and not the possible psychosocial impact of infertility and its treatment on couples and their families. Because there may be long-term effects of the drugs used to treat infertility by inducing ovulation (11), a study to assess such effects is being planned in the United States.

**Comparative Data from Various Countries**

At present, it is difficult to make direct comparisons of treatment cycles and pregnancy rates in different countries because data systems have been established quite recently and may be incomplete. Nevertheless, the available data can be used cautiously to compare pregnancy rates. The figures in Table 4 are based on data from all 20 units in Australia and New Zealand in 1987. Two small units treated women by GIFT but not by IVF. In the United Kingdom, 34 approved centers reported their results to the Interim Licensing Authority; of these, 26 centers treated infertility by both IVF and
Table 4. IVF and GIFT Oocyte Retrieval Cycles and Live-Birth Pregnancy Rates, Selected Countries, 1987

<table>
<thead>
<tr>
<th>Countries</th>
<th>Number of oocyte retrieval cycles</th>
<th>Live-birth pregnancies per 100 oocyte retrieval cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IVF</td>
<td>GIFT</td>
</tr>
<tr>
<td>Australia and New Zealand</td>
<td>6,796</td>
<td>2,109</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>6,983</td>
<td>2,658</td>
</tr>
<tr>
<td>United States</td>
<td>8,725</td>
<td>1,968</td>
</tr>
</tbody>
</table>

*Abbreviation: na = not available.

* Treatment cycles.
b Excludes one large center with incomplete data.
c Excludes 199 oocyte retrieval cycles with combined IVF and GIFT.

Sources: 26;31;40.

Do the available data permit some prediction of the future requirements for clinical services to treat infertile couples by assisted conception? Based on the figures for 1987, there are marked differences in the number of cycles of treatment between countries when differences in population are taken into account. Several assumptions must be made before making further comparisons between these results. As previously mentioned, there are no data available to compare the national prevalence of infertility and those infertile couples who can be treated by assisted conception. If we assume that these are similar in Australia and New Zealand, the United Kingdom, and the United States, and that the present clinical services in Australia and New Zealand are appropriate for the needs, we can predict substantial future growth of services in the United Kingdom and the United States.

As shown in Table 4, in 1987 there were about 9,000 cycles of treatment that reached the stage of oocyte retrieval in Australia and New Zealand. In the United Kingdom and United States there were about 10,000 and 11,000 oocyte retrieval cycles, respectively. However, there are marked differences in the population of these countries. In 1987, the United States (241 million) had about 12 times the combined population of Australia (16.0 million) and New Zealand (3.3 million), while that of the United Kingdom (56.9 million) was almost 3 times that of Australia and New Zealand (43). The proportion of women in each country in the age groups requiring treatment of infertility (25–44 years) was similar — Australia 30.2%, New Zealand 29.0%, United Kingdom 27.3%, and United States 30.9%.

These data suggest that if other countries develop their clinical services for assisted conception in a manner similar to the development of services in Australia and New Zealand, there could be at least a 10-fold increase in the United States, and a 3-fold increase in the United Kingdom, during a period of less than 10 years beyond 1987. However, the projected growth in the United States may be diminished by the relatively higher costs there and by lack of reimbursement by government and some health insurance funds.

It is not clear whether the demand for services will be sustained at the present level.
level as the waiting lists for treatment in Australia have diminished. However, the preliminary data for 1988 in Australia and New Zealand show a further increase in the number of cycles of treatment. Clinical pregnancies have increased by almost 30%, so it is by no means certain that an equilibrium has been reached. Beyond that, the future level of services for assisted conception remains unpredictable. It is possible that the backlog of eligible infertile couples may soon be overcome in some countries. On the other hand, with indications of an increasing incidence of pelvic inflammatory disease and tubal obstruction, future requirements for IVF services could actually increase.

COSTS OF TREATMENT

The main components of the cost of IVF and related health services are the investigation of infertility; the cost of procedures such as laparoscopy for oocyte collection; drugs and hormones; laboratory procedures; and the cost of hospital care, especially for multiple births. There is varying reimbursement from governments and health insurance for these costs. Pronatalist policies appear to be an important factor in some countries.

Two reports published in Australia in 1988 addressed the costs of IVF and related procedures (8,42). Nationally, the average cost of an IVF treatment cycle was estimated to be about $A3,600 (8). This figure included pretreatment assessment by the IVF unit, investigations after embryo transfer, and the cost of cycles that were not completed, but it excluded the costs of previous investigation and treatment of infertility by other medical practitioners and the costs of pregnancy care and childbirth. The total estimated costs for IVF and related services in 1987 was $A30 million—56% came from the government Medicare reimbursement for medical services, operative procedures, pathology tests, and drugs; health insurance funds contributed 24%; and the remaining 20% was paid by the treated patients.

In Western Australia, the average cost of an IVF treatment cycle ($A3,893) was slightly higher than nationally. The average cost of a GIFT treatment cycle was less (about $A3,607), but cycles in which embryos were transferred to the fallopian tubes were about 19% more ($A4,615). Compared to confinements after natural conception, and taking into account the costs of failed treatment cycles, the excess cost of each IVF confinement was estimated to be about $A57,000, while the excess cost for each GIFT confinement was almost $A30,000. Reflecting the high incidence of preterm and low birth weight infants after assisted conception, the mean cost for neonatal care of an IVF or GIFT infant was $A3,750 more than that for babies born after natural conception.

In the United States, based on a survey by the Office of Technology Assessment in November 1986, the average cost of IVF was estimated to be between US $4,000 and US $6,000 per treatment cycle (38). The median cost for an IVF cycle was US $4,688 and for GIFT, US $3,500. Total IVF expenditure in 1987 was estimated to be US $66 million.

FUTURE EVALUATION OF ASSISTED CONCEPTION

There is a dearth of accurate information worldwide about the prevalence of infertility and the proportion of infertile couples who may be eligible for treatment by assisted conception. Population-based studies are required to assess the pattern of clinical services, their costs, and the impact on couples of unsuccessful treatment.
Much of the present clinical and scientific research in assisted conception is directed towards improving pregnancy rates. The areas of research include methods of stimulating induction of ovulation without causing premature ovulation, altering the conditions for culture of embryos in the laboratory, and modifying uterine receptivity to enhance implantation of transferred embryos. Well-designed clinical trials with adequate sample size, often requiring the collaboration of several IVF units in multicenter studies, are needed to evaluate the effectiveness of these new methods of treatment.

Future registers of IVF and other forms of assisted conception should include evaluation of pregnancy rates and outcomes after the use of donor oocytes and frozen embryos, the influence of new methods of stimulating ovulation, the effect of the quality of embryos and oocytes on pregnancy rates and outcomes, and the possible benefits and hazards of drugs used to try to improve uterine receptivity. Because of rapid changes in treatment methods, it is essential that national data systems retain flexibility so that they can keep pace with the clinical trends. If the results of assisted conception are to be compared as a basis for developing policy and providing services, with subsequent international agreement on definitions is required to obtain uniform data and to ensure standardized reporting of results.

Until pregnancy rates are considerably higher than at present, the anticipated use of IVF for prenatal diagnosis, and possibly treatment, of various genetic disorders seems unlikely. It seems that prenatal diagnosis of conditions such as thalassemia, then induced abortion of abnormal fetuses, will continue as the most widely practiced option. However, some couples who are opposed to abortion may accept the reality of relatively low pregnancy rates and accede to prenatal diagnosis of preimplantation embryos, especially for X-linked recessive conditions such as hemophilia for which determination of fetal sex is important (15).

REFERENCES
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