Many countries now have registers of assisted conception that were initially set up to evaluate the effectiveness of treatment, to monitor pregnancy outcomes and the health of treated women, and to assess any immediate risks for the women and their children. World reports, based on information from national registers, have enabled international comparisons of the extent to which the various techniques of assisted conception are used to treat infertile couples, as well as comparisons of pregnancy outcome. The reports also provide comparative data on pregnancy rates in populations rather than in single in-vitro fertilization (IVF) centres. To determine whether newly introduced techniques such as intracytoplasmic sperm injection are associated with any increased risks of birth defects or other adverse outcomes, information notified to registers will often need to be supplemented by clinical reports or by linkage of data in IVF registers and other health data systems. Further efforts to improve the quality of information on assisted conception within each country and internationally need to be well supported so that the effectiveness of treatment and the outcomes of treated couples and their children can be evaluated properly.

Key words: assisted conception/IVF/registers

Introduction

The rapid growth of clinical and laboratory services for treating infertile couples by assisted conception that began in the early 1980s has continued into the early 1990s. The most recent international report on treatment in 1993 showed that more than 30 000 babies are now born world-wide each year after the use of these techniques (de Mouzon and Lancaster, 1995).

In Australia, which with France and Belgium has one of the highest rates in the world of treating infertility by assisted conception (Lancaster, 1992a), the number of resulting births has also increased. In 1993, almost 1% of national births occurred after assisted conception (Table I). About 1 in 175 singleton births, 9% of twins and almost half of all triplets and higher order multiple births were babies born after in-vitro fertilization (IVF) and gamete intra-Fallopian
Table I. Births after assisted conception in relation to total national births, Australia 1991–1993

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singletons</td>
<td>249 744</td>
<td>255 701</td>
<td>253 401</td>
<td>1137 (0.5)</td>
<td>1330 (0.5)</td>
<td>1445 (0.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Twins</td>
<td>6610</td>
<td>6692</td>
<td>6826</td>
<td>578 (8.7)</td>
<td>658 (9.8)</td>
<td>610 (8.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triplets</td>
<td>267</td>
<td>315</td>
<td>300</td>
<td>135 (50.6)</td>
<td>132 (41.9)</td>
<td>132 (44.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other multiple</td>
<td>13</td>
<td>18</td>
<td>5</td>
<td>4 (30.8)</td>
<td>9 (50.0)</td>
<td>13* (100.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All births</td>
<td>256 634</td>
<td>262 726</td>
<td>260 532</td>
<td>1854 (0.7)</td>
<td>2129 (0.8)</td>
<td>2200 (0.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Includes two sets of quadruplets that were not among the total birth registrations: one set was stillborn at 20 weeks gestation, the other set of three liveborn and one stillborn was registered as triplets.

transfer (GIFT). Assisted conception and other treatments of infertility by ovarian stimulation have had important effects on the demography of multiple births.

Much of the information about international trends and the outcomes of assisted conception treatment has come from national registers and other data systems developed over a period of more than a decade. To function effectively, these registers depend on the willing participation of many IVF centres in each country. Data from the registers complement the results from single IVF centres and collaborative studies, and also the findings from the wide-ranging scientific and social research involving many aspects of reproduction.

Development of national registers

The Australian register began collecting data in 1983. As the first IVF pregnancy in Australia had been conceived in 1979, and there had been just over 200 IVF pregnancies conceived by early 1983, it was possible to include information on these earlier pregnancies in the register. The first report, based on 309 IVF pregnancies, was published in 1984. Subsequently, the reports have included data from New Zealand, where the first IVF unit began treating infertile couples in 1983. At present, all 28 units using assisted conception in the two countries contribute summary data on treatment cycles and notify all pregnancies to the register.

Other countries also started registers in the mid-1980s. The initial report for the USA contained data for 1985 and 1986 (Medical Research International, The American Fertility Society Special Interest Group, 1988), while the French FIVNAT register has published its results since 1986. In the UK, the Voluntary Licensing Authority for Human In Vitro Fertilisation and Embryology published a brief summary of pregnancy rates for 1985 in its Second Report in 1987. A more detailed analysis of the outcome of pregnancies for the period 1978–1987 was published later, based on a register of children born after IVF and originally established in 1983 (MRC Working Party on Children Conceived by In Vitro Fertilisation, 1990). In recent years, many other countries have either started...
Registers of IVF and assisted conception

registers or provided pooled data for international reports. Countries that have now reported their results in journals or separate reports include Belgium, Canada, the Czech Republic, Japan, Latin American countries, the Nordic countries and Taiwan.

The emphasis in reporting results from national registers has varied considerably. The register for Australia and New Zealand has provided complete data on the immediate outcome of pregnancy, but for some years lacked information on the women treated and pregnancy rates. Other countries with established registers have tended to concentrate more on reporting pregnancy rates and factors such as age and cause of infertility that are associated with variations in these rates.

The French national register (FTVNAT) has been used to analyse the results for women treated by assisted conception and their pregnancy rates (FTVNAT et al., 1993). Other studies have included a survey of the sociodemographic characteristics of women considering IVF and those actually treated by IVF (de Mouzon and Bachelot, 1995); a study of a cohort of treated women, comparing the characteristics of those continuing and those ceasing treatment (de Mouzon and Rufat, 1995); seasonal variations in IVF pregnancy rates and related factors (Deffontaines and de Mouzon, 1995); a study of the outcome of pregnancies and children conceived by IVF in France between 1987 and 1989 (Rufat et al., 1994); and a comparison of IVF pregnancies and births with national results (FTVNAT, 1995).

International data on assisted conception

Initially data on IVF were obtained from individual IVF centres around the world and results were presented at international conferences and later published (Seppälä, 1985; Cohen et al., 1988). The first formal meeting of those responsible for national registers was held in Oxford in September 1990. This group is now known as the International Working Group for Registers on Assisted Reproduction. World collaborative reports for 1989, 1991 and 1993 were published in conjunction with IVF World Congresses held in Paris, France in 1991 and in Kyoto, Japan in 1993 and with the 15th World Congress on Fertility and Sterility held in Montpellier, France in 1995.

The extent of use of clinical services for treating infertile couples by assisted conception within a country depends on the prevalence of infertility, the proportion of couples who require such treatment, the availability and accessibility of these clinical services, their cost and whether funding is provided by governments and health insurance groups. Based on data from national registers, it has been shown that assisted conception is used relatively more in Australia, France and Belgium than in other countries (Lancaster, 1992a). In 1989, the ratios of the number of treatment cycles reaching the stage of oocyte retrieval per 100 000 women in the reproductive age group (25–44 years) were 357, 331 and 287 in Australia, France and Belgium respectively. These ratios were about double those in the UK and more than five times higher than those in the USA. As various countries
expand their services, these relative differences are likely to continue changing. Within Australia, there was less variability in ratios between the larger states, whereas in New Zealand the ratio was considerably less (AIHW National Perinatal Statistics Unit and Fertility Society of Australia, 1992).

Advantages of registers on assisted conception

These registers have some important advantages compared with studies of results in individual IVF centres. They provide population-based data on pregnancy rates, giving the average likelihood of achieving a pregnancy or live birth in all centres. This contrasts with pregnancy rates published in journals, which tend to be the optimal current results and may often give an unrealistic view of what is being achieved in most IVF centres. After consideration of the characteristics of each treated couple and how a particular IVF centre's pregnancy rates compare with national figures, infertile couples can be counselled about the possible outcomes of treatment.

Because registers obtain data from many IVF centres, there are larger numbers of treated women and pregnancies for analysing outcomes and evaluating the risks of some adverse outcomes. Depending on what information is collected in the register, this may enable the further study of specific pregnancy complications and comparisons with pregnancy outcome in naturally conceived pregnancies.

Limitations of registers on assisted conception

With their emphasis on reporting pregnancy rates and the immediate outcome of pregnancy, assisted conception registers may lack adequate information on complications resulting from ovarian hyperstimulation or pregnancy. The study of any long-term effects of treatment on the women or their children are usually beyond the resources of the registers.

Ovarian hyperstimulation syndrome is a significant side-effect occurring not infrequently in women treated with fertility drugs in assisted conception (Edwards and Brody, 1995). Its incidence and severity can be assessed only if registers obtain information on each treatment cycle as well as on pregnancies. Each country needs to adopt the same criteria for grading hyperstimulation if meaningful comparisons are to be made. Agreement on classifying the causes of infertility is also needed so that comparable data can be collected in each country.

The registers may have incomplete information on pregnancy complications because the details are not always readily available to those notifying the pregnancies from IVF centres. Such deficiencies can sometimes be overcome by linking data in IVF registers with those in other registers or data systems. In maximizing the amount of information that can be obtained by these methods at minimum cost, it is essential that parental requests concerning confidentiality of how their children were conceived are respected.
In some countries such as Finland, the analysis of IVF pregnancy outcome is enhanced by including in existing medical birth registers an item on the type of conception (Gissler et al., 1995). This enables ready comparison of IVF and other births, taking account of important risk factors for pregnancy outcome, and also the analysis of patterns of antenatal care, hospitalization during pregnancy and health care. By linking information on the type of conception to an existing cerebral palsy register, the risks of cerebral palsy in children born after assisted conception can be assessed (Kurinczuk, 1994).

To ensure compliance with the requirements for reporting data on treated couples and their pregnancies to national registers, the amount of information must be kept within reasonable limits. As the electronic transfer of data becomes more widely used, other information in computerized clinical and laboratory data systems can be included in the registers, but each additional data item must be justified.

Special studies are usually required to assess the long-term health of treated women and children born after assisted conception. These studies are often relatively expensive and may be difficult to organize because the women and children are widely dispersed in the community. Follow-up of women treated in one large Australian IVF unit (Venn et al., 1995) and of children conceived in two Melbourne IVF units (Halasz et al., 1993) was based on records held in those centres.

**Pregnancy rates**

Pregnancy rates are the main indicators of the effectiveness of assisted conception and are influenced by many factors, especially the maternal age, the number of embryos or oocytes transferred and the cause of infertility. Clinical pregnancy rates are still widely reported, but are increasingly being expressed in terms of the number of pregnancies resulting in live births. Published pregnancy rates are rarely adjusted to take account of maternal age and the other factors that may be important in comparing the results in different IVF units and countries (Lancaster, 1991), so these rates should be interpreted cautiously. Because of the larger number of treatment cycles included in the data of national registers, adjusted pregnancy rates can be published if there is complete reporting of risk factors for all treatment cycles (FTVNAT et al., 1993). Cumulative conception and live birth rates have been reported from single IVF centres (Tan et al., 1992), but there are major limitations in reporting such data from registers because identifying information for successive treatment cycles may not be available. Analyses of pregnancy rates that adjust for risk factors, and relate the number of live births following transfer of fresh and thawed embryos in successive cycles to the number of stimulated cycles, should be encouraged.
Table II. In-vitro fertilization cycles with more than three embryos transferred and incidence of multiple pregnancy, selected countries, 1993

<table>
<thead>
<tr>
<th>Country</th>
<th>Transfer cycles (n)</th>
<th>Cycles with more than three embryos transferred (%)</th>
<th>Total pregnancies (n)</th>
<th>Multiple pregnancy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>4678</td>
<td>2.6</td>
<td>555</td>
<td>20.7</td>
</tr>
<tr>
<td>Belgium</td>
<td>2817</td>
<td>11.0</td>
<td>594</td>
<td>33.0</td>
</tr>
<tr>
<td>Canada</td>
<td>2712</td>
<td>20.4</td>
<td>477</td>
<td>27.7</td>
</tr>
<tr>
<td>France</td>
<td>18,843</td>
<td>20.8</td>
<td>1526</td>
<td>29.2</td>
</tr>
<tr>
<td>Germany</td>
<td>4733</td>
<td>0.0</td>
<td>474</td>
<td>27.8</td>
</tr>
<tr>
<td>Greece</td>
<td>2881</td>
<td>36.5</td>
<td>442</td>
<td>34.2</td>
</tr>
<tr>
<td>Israel</td>
<td>4460</td>
<td>48.5</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Japan</td>
<td>6173</td>
<td>46.9</td>
<td>989</td>
<td>25.2</td>
</tr>
<tr>
<td>Latin America</td>
<td>2537</td>
<td>50.6</td>
<td>384</td>
<td>26.8</td>
</tr>
<tr>
<td>Sweden</td>
<td>3514</td>
<td>3.1</td>
<td>616</td>
<td>29.4</td>
</tr>
<tr>
<td>UK</td>
<td>11,942</td>
<td>0.0</td>
<td>2,294</td>
<td>29.2</td>
</tr>
</tbody>
</table>


Early pregnancy losses

Spontaneous abortion increases with maternal age, so high rates would be anticipated for women treated by assisted conception who are generally older and are more likely to have poor reproductive histories than women conceiving naturally. Lack of suitable comparison groups has limited studies of spontaneous abortion, but most registers report rates of ~20% in IVF pregnancies (de Mouzon and Lancaster, 1995), and some report maternal age-specific rates (Lancaster et al., 1995a). Ectopic pregnancy varies more between countries than does spontaneous abortion; the combined data in the world report for 1993 showed a rate of 4.3% (de Mouzon and Lancaster, 1995). Ectopic pregnancy is consistently more common in women with tubal factors treated by IVF (Lancaster et al., 1995a). An analysis of the Australian and New Zealand data up to 1985 showed that women who had previously achieved pregnancies by IVF had a more favourable outcome in their second IVF pregnancy with many fewer early pregnancy losses and relatively more live births (National Perinatal Statistics Unit and Fertility Society of Australia, 1987).

Multiple births

In IVF and GIFT, the usual practice of transferring two or more embryos or oocytes to achieve higher pregnancy rates results in a high incidence of multiple births. Many countries had IVF multiple birth rates well above 20% in 1993 (Table II), the highest rates occurring in Greece (34.2%) and Belgium (33.0%). The proportion of transfer cycles in which more than three embryos were transferred varied from none in Germany and the UK to 50.6% in Latin America and 48.5% in Israel.
While multiple pregnancy rates expressed as a proportion of all pregnancies reaching a gestational age of 20 weeks are high in assisted conception, an even greater proportion of the babies are from multiple pregnancies. Among 2846 IVF babies in the Australian and New Zealand cohort of 1992–1993, 30.7% were from multiple births (Lancaster et al., 1995a). The 15.8% of IVF pregnancies that were twins accounted for 26.6% of IVF babies, the 1.6% of triplet pregnancies for 4.0% and the one quadruplet pregnancy for 0.1% of these babies. Similarly, 42.3% of 2031 GIFT babies were from multiple pregnancies (35.0% from twins, 6.9% from triplets and 0.4% from other multiple births). In the UK, where there is a higher multiple birth rate after IVF than in Australia and New Zealand, 47.1% of 3033 babies from the 1992 cohort were from multiple births (Human Fertilisation and Embryology Authority, 1994).

Selective fetal reduction may be performed in an effort to avoid the high risks of fetal and neonatal death or morbidity among multiple births (Edwards and Brody, 1995). There is limited information on the extent to which selective reduction is used in this way. In France, this procedure was performed in 2.9% of pregnancies that resulted in births during the period between 1987 and 1991 (Dossier FIVNAT, undated). In Australia and New Zealand, selective fetal reduction was notified in only 25 (0.3%) of 9940 pregnancies resulting in births among conceptions between 1988 and 1993 (Lancaster et al., 1995a). In six of these cases, fetal reduction followed prenatal diagnosis of fetal abnormality.

Two distinct approaches seem to have been adopted to avoid high-order multiple births. Some countries, such as Australia, New Zealand, Germany, Sweden and the UK, have restricted by legislation or guidelines the number of embryos or oocytes transferred. Other countries do not have such policies and continue to transfer more than three embryos in up to half of all cycles.

Concern about the high fetal and neonatal death rates reported among multiple births by the national register resulted in the Fertility Society of Australia introducing a recommendation in 1988 that no more than three embryos or oocytes should be transferred in each treatment cycle. Since then, IVF and GIFT triplet rates have declined from >4% in the late 1980s to 1.5 and 2.4% respectively in 1993 (Lancaster et al., 1995a). There was less change in twin pregnancies, which declined from 20.4% in 1988 to 15.7% in 1993 for IVF but remained almost unchanged in excess of 20% for GIFT (23.5% in 1993).

Multiple births could be effectively decreased if two instead of three embryos or oocytes were transferred. In Australia and New Zealand in 1992–1993, more than half (59.0%) of 378 IVF twin pregnancies and 92.1% of 38 triplet pregnancies occurred after the transfer of three, or occasionally four, embryos (Lancaster et al., 1995a). Similarly, 77.5% of 355 GIFT twin pregnancies and 91.5% of 47 triplet pregnancies resulted from the transfer of three or more oocytes. While multiple births could be diminished substantially, overall IVF and GIFT pregnancy rates would also be lower.

Better information is needed on how frequently selective fetal reduction is performed to avoid multiple births and on the outcome of these pregnancies. In a recent study of 74 twin pregnancies continuing beyond 10 weeks, the mean
Table III. Preterm birth (%) by maternal age in singleton in-vitro fertilization (IVF) births (Australia and New Zealand, 1992-1993) and all births (Australia, 1992)

<table>
<thead>
<tr>
<th>Maternal age (years)</th>
<th>Singleton IVF births</th>
<th>All births, Australia, 1992</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Births n</td>
<td>20-31 weeks (%)</td>
</tr>
<tr>
<td>&lt;25</td>
<td>38</td>
<td>5.3</td>
</tr>
<tr>
<td>25-29</td>
<td>425</td>
<td>5.2</td>
</tr>
<tr>
<td>30-34</td>
<td>859</td>
<td>3.0</td>
</tr>
<tr>
<td>35-39</td>
<td>553</td>
<td>4.0</td>
</tr>
<tr>
<td>≥40</td>
<td>98</td>
<td>4.1</td>
</tr>
<tr>
<td>All agesa</td>
<td>1973</td>
<td>3.9</td>
</tr>
</tbody>
</table>

Sources: Lancaster et al. (1995a,b).
aIncludes unstated maternal age.

Table IV. Preterm birth (%) by cause of infertility in singleton in-vitro fertilization births (Australia and New Zealand, 1992-1993)

<table>
<thead>
<tr>
<th>Cause of infertility</th>
<th>Births n</th>
<th>20-31 weeks (%)</th>
<th>32-36 weeks (%)</th>
<th>20-36 weeks (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubal</td>
<td>594</td>
<td>3.9</td>
<td>8.6</td>
<td>12.5</td>
</tr>
<tr>
<td>Male</td>
<td>454</td>
<td>4.0</td>
<td>10.1</td>
<td>14.1</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>128</td>
<td>3.1</td>
<td>13.3</td>
<td>16.4</td>
</tr>
<tr>
<td>Multiple</td>
<td>441</td>
<td>3.4</td>
<td>10.5</td>
<td>13.9</td>
</tr>
<tr>
<td>Unexplained</td>
<td>221</td>
<td>4.5</td>
<td>13.6</td>
<td>18.1</td>
</tr>
<tr>
<td>All causesa</td>
<td>1973</td>
<td>3.9</td>
<td>10.7</td>
<td>14.6</td>
</tr>
</tbody>
</table>

Source: Lancaster et al. (1995a).
aIncludes 135 births with 'other' or 'not stated' causes of infertility.

gestational age of the 32 pregnancies in which selective reduction had been performed was 33.8 weeks compared with 35.7 weeks in the other 42 pregnancies (Steinkampf et al., 1995). Birthweight was also decreased and fetal growth seemed impaired.

**Preterm birth**

A high incidence of preterm birth in IVF pregnancies was noted in the first Australian report (National Perinatal Statistics Unit and Fertility Society of Australia, 1984; Australian In Vitro Fertilization Collaborative Group, 1985), associated not only with multiple births but also with singleton births. This pattern has persisted, and high rates of preterm births in singleton pregnancies are found in all maternal age groups (Table III) and in the pregnancies of women treated for all causes of infertility, even when infertility is caused by male factors (Table IV). In most maternal age groups, IVF singleton infants are more likely to be born at gestational ages of 32-36 completed weeks than are infants in the general population (Lancaster et al., 1995b) (Table III). The differences between
Table V. Preterm birth\( ^a \) in singleton in-vitro fertilization pregnancies, selected countries, 1991 and 1993

<table>
<thead>
<tr>
<th>Country</th>
<th>1991</th>
<th>1993</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pregnancies (n)</td>
<td>% Preterm</td>
</tr>
<tr>
<td>Australia/New Zealand</td>
<td>433</td>
<td>14.1</td>
</tr>
<tr>
<td>Belgium</td>
<td>298</td>
<td>10.1</td>
</tr>
<tr>
<td>France</td>
<td>941</td>
<td>9.0</td>
</tr>
<tr>
<td>Germany</td>
<td>412</td>
<td>12.9</td>
</tr>
<tr>
<td>Greece</td>
<td>298</td>
<td>33.6</td>
</tr>
<tr>
<td>Japan</td>
<td>906</td>
<td>7.6</td>
</tr>
</tbody>
</table>

Sources: Cohen et al. (1993); de Mouzon and Lancaster (1995).

IVF and population births are more pronounced below 32 weeks; 3.9% of singleton IVF births occurred at gestational ages of 20–31 weeks compared with only 1.4% of all births, and IVF preterm births were more than twice as high in every maternal age group. These findings suggest that factors other than maternal age and the cause of infertility are important in determining the high rate of preterm birth in singleton IVF pregnancies and that periconceptional factors, as well as pregnancy complications, should be considered.

International data have confirmed that preterm birth in singleton IVF pregnancies also occurs commonly in other countries, but the incidence varies markedly (Table V). Defining preterm birth as a gestational age at birth of 20–36 completed weeks and comparing data for selected countries published in the international reports for 1991 and 1993 (Cohen et al., 1993; de Mouzon and Lancaster, 1995), there was as much as a 4-fold difference between Greece (which had a high incidence) and Japan (which had a relatively low incidence). The consistent differences in singleton preterm births between countries indicate that there may be significant avoidable factors.

Low birthweight

Low birthweight is more common in assisted conception births than in the general population; this is partly attributable to multiple births but also occurs in singletons (Australian In Vitro Fertilization Collaborative Group, 1985; de Mouzon and Lancaster, 1995). Various reports and other studies based on national registers have examined the relationship between risk factors such as maternal age, cause of infertility, number of embryos transferred, plurality, pregnancy complications and the outcomes of preterm birth, low birthweight and fetal growth (National Perinatal Statistics Unit and Fertility Society of Australia, 1987; Doyle et al., 1992; Gissler et al., 1995). Further studies are needed, not only in the main treatment groups of IVF and GIFT, but also for specified subgroups of babies such as those born after embryo freezing and thawing and/or intracytoplasmic sperm injection. Low birthweight was less common in 634 singleton
Table VI. Proportion of in-vitro fertilization (IVF) and gamete intra-Fallopian transfer (GIFT) perinatal deaths occurring among singleton and multiple births

<table>
<thead>
<tr>
<th>Type of conception</th>
<th>Plurality</th>
<th>Fetal deaths n (%)</th>
<th>Neonatal deaths n (%)</th>
<th>Perinatal deaths n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVF</td>
<td>Singleton</td>
<td>29 (54)</td>
<td>18 (50)</td>
<td>47 (52)</td>
</tr>
<tr>
<td></td>
<td>Twin</td>
<td>20 (37)</td>
<td>14 (39)</td>
<td>34 (38)</td>
</tr>
<tr>
<td></td>
<td>Triplet</td>
<td>1 (2)</td>
<td>4 (11)</td>
<td>5 (6)</td>
</tr>
<tr>
<td></td>
<td>Other multiple</td>
<td>4 (7)</td>
<td>-</td>
<td>4 (4)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>54 (100)</td>
<td>36 (100)</td>
<td>90 (100)</td>
</tr>
<tr>
<td>GIFT</td>
<td>Singleton</td>
<td>6 (21)</td>
<td>5 (16)</td>
<td>11 (19)</td>
</tr>
<tr>
<td></td>
<td>Twin</td>
<td>13 (46)</td>
<td>15 (48)</td>
<td>28 (47)</td>
</tr>
<tr>
<td></td>
<td>Triplet</td>
<td>8 (29)</td>
<td>10 (32)</td>
<td>18 (31)</td>
</tr>
<tr>
<td></td>
<td>Other multiple</td>
<td>1 (4)</td>
<td>1 (3)</td>
<td>2 (3)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>28 (100)</td>
<td>31 (100)</td>
<td>59 (100)</td>
</tr>
</tbody>
</table>

Source: Lancaster et al. (1995a).

infants born after embryo freezing (8.9%) than in all singleton IVF infants (14.7%) (AIHW National Perinatal Statistics Unit and Fertility Society of Australia, 1993).

**Perinatal mortality**

Multiple births and preterm singleton births are important factors contributing to high perinatal death rates among infants born after assisted conception (National Perinatal Statistics Unit and Fertility Society of Australia, 1985; Australian In Vitro Fertilization Collaborative Group, 1988). Based on a lower gestational age of 20 weeks for fetal deaths and including neonatal deaths within 28 days of birth, the perinatal death rate of 47.5 per 1000 births for the first 1138 IVF births in Australia and New Zealand was about four times higher than the national rate of 11.8 per 1000 births in 1985 (Australian In Vitro Fertilization Collaborative Group, 1988). The most recent data for these two countries show lower perinatal death rates for IVF and GIFT of 31.6 and 29.0 per 1000 births respectively (Lancaster et al., 1995a), but these rates are still much higher than in other births.

In Australia and New Zealand, despite the policy of limiting the number of embryos or oocytes transferred, multiple births still account for a high proportion of all perinatal deaths (Table VI). In 1992–1993, 48% of 90 IVF perinatal deaths and 81% of 59 GIFT perinatal deaths occurred among multiple births (Lancaster et al., 1995a), compared with only 10.0% in all births in Australia in 1990–1992 (Lancaster et al., 1995b). In the UK, where perinatal deaths include fetal deaths of at least 24 weeks gestation and deaths of liveborn babies in the first week, 63% of 68 IVF perinatal deaths were in multiple births (Human Fertilisation and Embryology Authority, 1994). Thus, while these countries have effectively reduced the transfer of more than three embryos, twins and triplets still contribute the majority of perinatal deaths among births after assisted conception.
Major congenital malformations are anatomical defects or chromosomal abnormalities that are present at birth and are either lethal or significantly affect the individual's function or appearance. They occur in 2–3% of all births. Because notification of minor malformations is often incomplete, they are excluded from most studies unless all children have been examined carefully. There have been few studies of specific types of congenital malformation among children born after IVF (Lancaster, 1987; MRC Working Party on Children Conceived by In Vitro Fertilisation, 1990; Lancaster, 1992b; Liebaers et al., 1995). In such studies, many factors that might be associated with varying risks of malformation need to be considered, including maternal and paternal age, the underlying causes of infertility, ovarian stimulants and other drugs used during the treatment cycle, various laboratory procedures and genetic factors that cause male infertility. As well as this heterogeneous group of risk factors, there are also significant problems in ascertaining malformations, in ensuring that they are all notified, in determining what is a suitable comparison group and in achieving an adequate sample size to detect differences in the risk of specific malformations. Malformation rates are likely to be underestimated in those registers where reliance is placed on routine notifications that are not backed up by verification from other sources. Unless ascertainment of congenital malformations is comprehensive, pooling of the data from the various countries is not justified. Those responsible for national IVF registers should take advantage of possible collaboration with groups involved in the epidemiology of birth defects.

Except in studies where all children are examined systematically, the organization of clinical services for treating infertile couples often militates against the complete and accurate ascertainment of birth defects. The care of women at around the time of conception and in early pregnancy may be undertaken in IVF centres, but subsequent care in pregnancy by obstetricians and midwives often occurs in other hospitals and private practices. At least in some countries, assisted conception is now widely perceived as commonplace, possibly affecting the notification of malformations. Those responsible for national registers must rely on the interest and goodwill of clinic coordinators, scientists and gynaecologists working in IVF centres. In turn, there also needs to be good communication from doctors who refer their patients to IVF centres for treatment.

The completeness of ascertainment of congenital malformations varies with the age to which children in a birth cohort are followed up and the extent of prenatal assessment, and may differ from that in the general population. High multiple pregnancy rates after assisted conception increase the likelihood of the selective fetal reduction of malformed fetuses diagnosed prenatally. Notification of these cases may be incomplete, and sometimes diagnoses based on an ultrasound examination may be difficult to confirm.

An analysis of data on trisomy 21 and other maternal age-dependent chromosomal abnormalities is complicated by whether or not terminations of pregnancy after chorionic villus sampling or amniocentesis are included. Because these
abnormalities account for a significant proportion of spontaneous abortions, they are likely to be detected in some IVF spontaneous abortions examined cytogenetically. It is then necessary to decide how all chromosomal abnormalities can be compared with data for the general population.

Additional information on malformed infants is often required to verify specific diagnoses and to determine whether notified congenital malformations are isolated, multiple or associated with a chromosomal abnormality or some other recognized syndrome. For example, hydrocephalus may be congenital or may develop as a postnatal complication, especially in preterm infants; cardiac murmurs may be innocent or a sign of congenital heart defects; kidney abnormalities may include a spectrum from minor dilatation of the ureters to bilateral absence of the kidneys; and bowel blockage may be a result of intestinal atresia, cystic fibrosis (which is not a congenital malformation) or postnatally acquired necrotizing enterocolitis in a preterm infant. A condition such as holoprosencephaly may be an isolated defect, may occur with bilateral cleft lip and palate in a chromosomally normal infant or may be associated with cleft lip and palate in trisomy 13.

In IVF births conceived after intracytoplasmic sperm injection, there may be an increased risk that genetic diseases or chromosomal abnormalities affecting male fertility are transmitted or that sex chromosomal abnormalities may result from fertilization by abnormal spermatozoa. In general, obtaining reliable data on these conditions poses an even more substantial problem than ascertaining congenital malformations. Many do not have an abnormal phenotype that can be recognized at birth. Unless prenatal or postnatal cytogenetic examination or other relevant tests are performed, these conditions associated with male infertility may not be diagnosed until adolescence or later. In attempting to gain new insights into the role of paternal factors in causing birth defects, it is essential to determine the parental origin of chromosomal abnormalities and at which meiotic division they occurred.

In Australia and New Zealand, the incidence of major congenital malformations among infants conceived between 1979 and 1993 was 2.5% for IVF and 2.7% for GIFT (Table VII). Malformation rates were slightly higher in singleton than in multiple births.
A high incidence of spina bifida was reported among the first 1694 IVF births in Australia and New Zealand (Lancaster, 1987). The high rate of neural tube defects has persisted among >15 000 births (Lancaster and Shafir, 1996). In a study of 1581 births in the UK, there were four cases of anencephalus and three cases of spina bifida, more than the expected number of each malformation (MRC Working Party on Children Conceived by In Vitro Fertilisation, 1990). Similar findings have not been reported from other registers, but it is unclear whether there is complete reporting of congenital malformations and whether specific types of malformation have been analysed separately in other countries. Further epidemiological and laboratory studies are needed to confirm these findings and to determine whether the occurrence of neural tube defects in assisted conception pregnancies is folate-dependent and whether the majority of these serious malformations are preventable. Although no causal link has been established between assisted conception and neural tube defects, it seems prudent to ensure that periconceptional folic acid supplements are given to all women being treated by assisted conception.

Cancer in treated women and their children

Now that so many women have been treated by assisted conception, it is inevitable that various diseases will increasingly be noted among them. Reports of ovarian and breast cancer in treated women, and concern that these cancers could be causally related to the drugs used for ovarian stimulation, led to a study in Melbourne, Australia of >10 000 women who had registered at one IVF centre over a 15 year period. Initial results in this study performed by linking IVF and cancer registry records showed that women in an FVF programme did not have a higher risk of breast and ovarian cancer (Venn et al., 1995). Uterine cancer was more common but was not related to treatment with fertility drugs. As the number of women with some types of cancer was quite small, and the interval between treatment and when the study was performed was relatively short for most women, further studies of this association between fertility drugs and cancer are needed. In countries where details of treated women are placed on a national register, this would facilitate such studies. Regarding the hypothesis that the risk of ovarian cancer might be increased by ovarian stimulation (Fathalla, 1971), it should be noted that the number of oocytes collected by ultrasound guidance or laparoscopy in Australia and New Zealand have increased considerably in recent years (Lancaster et al., 1995a).

Cancer has also occurred among children born after IVF in Australia (White et al., 1990). In that initial report of three children with neuroectodermal tumours, two had a neuroblastoma and one had a medulloblastoma. Only one of these children had been notified directly to the register of assisted conception. Since then, two further cases of neuroblastoma have been notified, one occurring after subzonal insemination. Another child diagnosed as having acute lymphoblastic
leukaemia at 10 weeks of age has also been notified. These cases occurred among >15 000 children born after assisted conception.

As with cancer in women treated by assisted conception, childhood cancer cannot be completely ascertained by registers established to obtain information on treated women and their immediate pregnancy outcomes. Systematic studies of cancer among children born after assisted conception are needed to determine whether their risk differs from that of the general population. This could be achieved by study designs similar to that for women treated in IVF clinics, linking records in the IVF clinics with those in cancer registries.

**Future requirements of registers**

New developments in fertility drugs and the techniques used to treat infertility have been a marked feature of assisted conception over a period approaching two decades. The introduction of intracytoplasmic sperm injection has demanded better information about male causes of infertility and the outcome of treatment. Freezing of immature oocytes and ovarian tissue, in-vitro maturation of oocytes and preimplantation diagnosis are other recent developments that will require an evaluation of their outcomes.

Continuing international collaboration through the International Working Group for Registers on Assisted Reproduction and various regional networks in Europe, Latin America and the Asia-Pacific region is essential to build on the experience to date, to develop registers in other countries and to ensure that standard definitions are used to report pregnancy rates and outcomes. By providing timely, population-based data, registers of assisted conception can be accountable to infertile couples seeking treatment, to the IVF teams that treat these couples and to the wider community.

Although much is said about the need for the study of outcomes and follow-up, funding of these studies has often proved difficult to obtain. There are major investments in developing fertility drugs and providing clinical and laboratory services, but relatively little in evaluating outcomes and risks.

**Conclusions**

National registers have proved to be effective in evaluating pregnancy rates and pregnancy outcome after assisted conception. International comparisons of these data show varied clinical practices for treating infertile couples and differences in the pattern of delivery of clinical services. Such international comparisons also highlight variations in pregnancy outcome, in particular the occurrence of multiple births and their relationship to policies on the number of embryos or oocytes transferred in IVF and GIFT cycles. New hypotheses are needed to explain unusual findings, especially the high rate of preterm birth in singleton
Registers of IVF and assisted conception

IVF pregnancies and the high rate of neural tube defects and possibly other congenital malformations.

Data in national registers have been important in analysing trends in IVF treatment and outcomes over a period of more than a decade. These results serve as a constant reminder that the remarkable heterogeneity of infertile couples and the many different types of treatment and procedure must always be considered in trying to explain their outcomes.

By regularly analysing and presenting detailed data on treated women and their pregnancies, those responsible for registers of assisted conception can inform prospective parents, medical practitioners, scientists and the general community about outcomes and possible risks. Such information also encourages those with ideas about the findings to develop and test explanatory hypotheses.

References


P.A.L. Lancaster


Discussion

Nygren: Just a week ago, we had permission to launch a study on our birth register where we will be able to pick out two control groups as you were discussing. One comes from the general population and one from those pregnancies identified as having had previous fertility problems, but not having had ART procedures.

As Paul Lancaster has pointed out, although multiple pregnancy rates are going down, we still have a high proportion of twins. Even in singletons we see a high proportion of risks and we certainly see many in twins. Is it satisfactory to aim at having twins? Is the conception of twins acceptable?

Van Steirteghem: We will have part of the answer this afternoon, because Doyle will discuss the outcome of multiple pregnancies.

Simpson: It comes down to your discussion with the patients. At least in the USA by and large, most ART patients are comfortable with twins. They are not comfortable with triplets. Beyond that, we are imposing our own beliefs and I think we can probably be a bit aggressive when it comes to quadruplets and quintuplets. When the data is presented, there is obviously a higher frequency of complications in multiple births, and patients must be told of the likelihood of twins occurring. They can then share in some of the decision-making process. I do not think there is a simple and complete answer.

Lancaster: Just to answer the initial comment. It is important to be aware of any other existing data systems in some countries that can possibly be linked to the IVF registries. A nice study from Finland was published in 'Human Reproduction' recently using the medical birth register to compare IVF and other births. The Nordic countries, with their unique personal identifiers, are in a much better position to do that sort of study. We should take advantage of such situations to look at not only pregnancy outcome in general, but also the risks of malformations and childhood cancers.

Simpson: Could you comment on the question of the frequency of malformations in twins in general? Dizygosity, for example, is believed by many investigators to involve an increase in the frequency of malformations in twin gestations. You obviously did not see that in your data, but what are your thoughts about it?

Lancaster: Unfortunately, most population studies do not have good information about zygosity. This can be looked at indirectly by examining the relative proportion of like and unlike-sex infants. Most studies indicate that the high rate of malformation in twin pregnancies is because of monozygotic twins; in general in assisted conception, there is some evidence to suggest that monozygotic twinning might arise occasionally. Of course, after assisted conception most of the twins are dizygotic and that is why we have a low malformation rate compared to the singletons. But why is the malformation rate actually lower in twins? That might be just due to differences in maternal age and also small numbers.

Edwards: The point about twins has been summarized very nicely by a debate in Human Reproduction recently. It was stated by N. Gleicher and his colleagues...
Discussion

that in his practice many couples wish to have twins. They settle their family straight off and they do not want to come back for more IVF. Their article was followed by two or three letters rather supporting this case. When we talk about twins, we must realize that some couples desire twins and it may be far better for them to have a twin birth than to have two singletons. So we are always going to have to face this problem and it is very important to find out what the patients desire.

Tarlatzis: One of the reasons that Simpson and Lancaster pointed out is the way the register is compiled, which is common in other countries too. It is done on a voluntary basis so the centres may or may not have very accurate records of the patients and the babies born. It is also true in other countries, for example in France which has one of the largest registries, that it is very frequently impossible to follow-up what is happening to the babies. The patients travel a lot; they disappear; they go to different gynaecologists. Unless there is a system that meticulously follows the babies, we are bound with inaccuracies.

The second point concerns prematurity in singletons. I can testify for my country that many patients wish to deliver prematurely, or are prematurely delivered by gynaecologists by elective caesarean section. I do not know if a factor of high anxiety in using pre-term delivery plays a role as well, but I know that many caesarean sections are done prematurely, just to be on the safe side.

Lancaster: These factors may contribute a little. It is difficult to explain the difference between population data and assisted conception data for preterm births less than 32 weeks, unless you intervene really early in Greece.

Simpson: The other issue is that there is a very high caesarean section rate because of physician and parental anxiety. Presumably, in general, you have a lower prematurity rate because you have miscalculated the length of gestation, and that should be less of an issue here.

Edwards: When we examine what we do in the embryology laboratory, it is clear that we are dealing with an astonishing period of genetic activity in the embryo. First of all, there is the imprinting situation which appears to happen in the late blastocyst or later. The fragile X amplification also occurs near here, but we are not exactly sure when. There are papers in ‘Mutation Research’ on the fact that the late pronuclear stage is very highly susceptible to teratogenesis when exposed to high levels of carcinogens and other compounds. Do you think that we lose many of these anomalies in early pregnancy? Is the frequency of the defects that we are actually inducing in IVF lowered by the fact that many are aborted and lost early in pregnancy? Should we look closely at the early loss of preimplantation or early post-implantation embryos, of which there are probably no data or statistics on natural conception? And finally, do you think that this astonishing event in cattle called the large calf-syndrome, has anything to do with IVF? How is it that veterinarians have found these cases whereas we have not in our practice?

Simpson: I cannot really comment on the latter, and hand it back to you.

Edwards: I think there is no question that we lose enormous numbers of pregnancies during IVF. Everybody knows of the high frequency of monosomies...
and trisomies. Furthermore they are the only stage in which we recognize many of these anomalies, particularly the nullisomies as well as certain relatively lethal trisomies. It would be fascinating to try to recover and analyze embryos that have persisted through implantation after IVF, although of course it is not possible to do easily, to see what the effects of continued perturbation of an in-vitro system would be. It would be a dauntingly difficult investigation to make any sense out of. Nonetheless, many unusual genetic conditions must certainly arise in vitro. There may a high prevalence of such mutations and many of these embryos would be those failing to implant. This would be another example of Nature protecting against our mistakes. The bottom line is that we have produced many babies that we are proud of, but we may not exactly know all the reasons why or where many anomalies have been lost.

*Simpson:* There have been many reports now on the high frequency of mosaicism, chromosomal mosaicism, for example in IVF embryos. I know of no comparable data on in-vivo embryos.

*Edwards:* When Lancaster presented his analysis, it was on data which has no secondary analysis. We are never able to analyze co-variables or assess regression equations which may penalize certain clinics who aim for high success rates, eg. those that stop treating patients at age 35, whereas another clinic goes on to 45. We obtain large amounts of data and some evidence of variations but they are never explained. I honestly think it is no longer helpful to carry on publishing vast amounts of arithmetic data. It is time for more sophisticated analyses. The HFEA in London has established a clinic-grading system based on a complex multi-regression equation and UK clinics are now judged by this equation whether we like it or not. Is it not time that this sort of statistical analysis was done by yourselves who obtain world data on a massive scale that could indicate variability between clinics and maybe variabilities between countries. Would it be much clearer to have this sort of statistical analysis rather than these endless slides on arithmetic data?

*Lancaster:* I tried to emphasize at the start of my presentation that there are some deficiencies in the data we are collecting in national registries and also in making international comparisons. Indeed, in the Australian and New Zealand reports, we do analyze outcomes by maternal age and the cause of infertility. Certainly, you could do a more sophisticated logistic regression analysis and we have done that occasionally in some of our published articles. In terms of studying the malformations, we do not always have enough cases to analyse by maternal age group, cause of infertility and whether it is IVF or GIFT. There can be over-analysis of data that is limited in terms of the actual numbers.

Regarding the international data, we are only just starting. It would be wonderful if we could do this type of sophisticated data analysis that you are recommending, but while there has been a large investment in drugs and operating the clinical services for treating infertile patients, the amount of funding that has gone into evaluating the outcome of that treatment is pitiful. That is part of the problem. At present with the resources that we have, we really cannot do anything beyond the current descriptive reports. We have applied to the European Commission
Discussion

and to some of the pharmaceutical companies. The more influence that prominent people bring to bear on ensuring whether in the UK or internationally, that there is adequate funding to do these studies the more likely it is that they will be done. We are aware of the data limitations and the relevant risk factors and there are epidemiologists and gynaecologists who are willing to analyze the data, but there are no resources beyond the effort that these individual people are prepared to put into it.

Edwards: Is there enough data on certain aspects of IVF to do some analyses, for example on implantation rates and abortion rates? You may not have enough data to do analysis on congenital malformations but, for example, I think the data on neural tube defects in Australia do not appear to be borne out in other countries. Some sort of analysis is urgently needed on this point because the advice given to patients could be quite misleading. There is considerable room for improvement and if nothing else, the HFEA could do it on their results in Britain. Similar analysis can probably apply to other systems.

Lancaster: In Australia I have spent many years trying to convince clinical colleagues that we ought to be collecting cycle-specific data and not just information on pregnancy outcome. It is only quite recently we have obtained agreement on reporting all treatment cycles. Thus, we have been unable to analyze pregnancy rates by maternal age and cause of infertility, much as we would like to.

Edwards: What advantages did you see in such an analysis?

Lancaster: I think analyzing the pregnancy rates in the mid-nineties is at a stage similar to that in evaluating where we were at perinatal mortality rates several decades ago. International comparisons and perinatal mortality rates showed differences that could be partly attributable to definitions, as well as to other factors. Many of us involved in running IVF registries would like to see only live-birth pregnancy rates being published, because clinical pregnancy rates are usually not meaningful to infertile couples. It is really a question of building up the appropriate information within national registers and so far we are not in a position to report more detailed information internationally. But at least we can give a figure. We can say that one in 10 or one in eight or one in 15 IVF cycles will result in a live-birth, and that one in five GIFT cycles result in a live-birth, depending on the woman’s age and other factors.

Simpson: Just a follow-up on the neural tube defects. At least in many countries, neural tube defects would be easiest to monitor because of the ease of detecting these defects.

Lancaster: In the UK, data are available for the first thousand or so births but information on subsequent births was not ascertained in the same way. In Australia, we have had consistent reporting of malformation over the years. We are reluctant to pool international data on birth defects because of this variable ascertainment. The figures on birth defects published in the world report have major limitations.

Silber: We have observed a 29% abortion rate in the MESA and TESE cases with normal spermatogenesis. We do not suspect any specific defects in the sex
chromosomes with normal spermatogenesis in pregnancies and we do not expect any problems in the wife other than routine population noise because it is clearly an azoospermia situation. What do you think of this? It does not seem to fit in to an idea that we have of abnormal males in terms of spermatogenesis, nor does it seem that we have a specifically abnormal population of females. When we limit analysis to women under the age of 37, the abortion rate is 29%, which seems a little high.

Could you clarify what you feel about the possibility that we have or do not have an increased incidence of sex-chromosomal anomalies in these ICSI patients? I thought that you indicated that this feature was not so important?

Simpson: I think that until you know all of the confounders that it is difficult to make any comment about whether the 29% rate is increased in general, or if it is due to the small sample size that exists. I would point out that there are some paternal contributions to trisomies. About 5% of trisomy 13 and 18, are of paternal origin, so there are some things that can occur that need investigation. The numbers are small at present.

Lancaster: Our data showed that after taking account of maternal age, which is the main confounder for spontaneous abortion, there were no differences between ICSI and other IVF pregnancies in the rate of spontaneous abortion.

Nygren: About the twins, I think the answer I received was that twins are alright, because the parents like twins. That is a bit weak, I wish to emphasize that national registries and collection of data are very important. Exactly what is the increased risk for malformations etc? This question has to be put, and it has to be discussed in much more detail than just to tell us that this is what parents want.