Infertility in the third millennium: implications for the individual, family and society: Condensed Meeting Report from the Bertarelli Foundation’s Second Global Conference

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Primary infertility is a key issue in the developed world, while the developing world has high rates of secondary infertility. The impact of HIV/AIDS on fertility is insufficiently explored. One of the most important barriers to access to infertility treatment is cost; at the same time the role of social and cultural factors in restricting access should not be underestimated. IVF has become the standard therapy for female infertility, and ICSI for infertility of the male partner. However, the use of these therapies should not be initiated without a thorough investigation and, whenever possible, individual diagnosis of the underlying causes of infertility. Multiple gestation remains one of the most challenging and controversial issues in the treatment of infertility. Current IVF practices are often blamed for this; in this respect, attention should also be focused on the role of ovarian stimulation in ovulation induction. National guidelines and national registries for assisted reproductive technology (ART) are becoming more widespread and are expected to play an important role in promoting best practice in ART in the future.

Key words: assisted reproductive technologies/infertility/ICSI/multiple births/reproductive health

Introduction

A survey of cultural attitudes around the world shows that personal suffering associated with infertility is an ancient part of the human condition (‘Give me children, or I shall die!’—Rachel, Genesis 30:2), often compounded by a strong social stigma toward infertile men and women. In recent years progress in medical technology has offered hope to many infertile couples, especially in the developed world. However, the progress that has been made has raised new medical, ethical and social issues that require attention not only from health professionals but also from society as a whole. The Bertarelli Foundation meeting began with defining key terms in infertility, with the aim of encouraging greater clarity in discussions between different disciplines. This was followed by a discussion of the different perspectives of the developed and developing worlds and particularly the barriers to access to treatment for those who need it. Barriers to access are often financial and the economics of infertility treatment were explored in some detail. The emergence of HIV infection and AIDS has implications for fertility that are complex and insufficiently studied.

At the level of the family, the conference discussed the current management of both male factor and female factor fertility. Multiple gestation is a continuing challenge associated with fertility treatment and one that can have severe consequences not
only of the health of both mother and child but also in terms of stress on the family due to other factors, such as financial considerations. The conference also heard data from a new multi-centre study of the physical and psychological development of children born following ICSI.

Future progress in overcoming the challenges facing infertile couples and their health professionals will stem from international and interdisciplinary co-operation in exchanging information and establishing guidelines for best practice. The present meeting and its report represent an attempt to stimulate awareness of the key issues and their implications both at the level of health policy and at the level of the individual infertile couple.

Defining key terms in infertility

Infertility and related terms have ambiguous meanings in different disciplines. In demography, the terms fertility and infertility refer to the actual reproductive performance in a purely descriptive manner. These terms are used according to whether there was actual childbearing or not during a certain period of time, not taking into account whether or not the couple (woman) wished to have a child. For example, if no birth has been recorded in a married woman for 2 years, she is designated as being infertile during a 2 year period, also if she used birth control because she did not want to have children. The infertility is either primary (no child before) or secondary (one or more children before). Permanent infertility extends to the end of the childbearing years, irrespective of whether the woman was voluntarily or involuntarily childless. The capacity of a couple (a woman) to produce a live birth is called fecundity, which term also may be used to define the ability to conceive. The complete lack of that capacity is called infecundity or sterility. Infecund in demography has the same notion as the term infertile in common language, meaning unable to conceive or to have a child with the connotation of barren or sterile.

In contrast, in reproductive medicine the term infertility is used for women (or couples) who have had unprotected, regular intercourse for ≥1 years and who fail to achieve a pregnancy. A 1 year threshold of infertility has more or less become the gold standard in clinical medicine, but 2 years is often used in epidemiological studies whereas in developing countries 5 years is often taken into account.

Primary infertility is the term used in reproductive medicine for a woman (couple) who failed to achieve a pregnancy for 1 or 2 years and who was never pregnant before. Secondary infertility is the term applied to women who meet the criteria for primary infertility but at some time in the past have been pregnant. In reproductive medicine, the term infertility can be used in a descriptive manner to define the situation in women (couples) who are unable to conceive or have a pregnancy leading to live birth, during ≥1 years. But it has also absorbed the meaning of the term as used in common language in the sense of impossible to conceive, synonymous with the demographic term infecundity.

Various discussions during the conference were focused on the necessity to have less ambiguous definitions.

Trends in permanent infertility in the developing world

In most developing countries, the proportion of permanently infertile women is low compared with that reported in developed countries. Data from the Demographic and Health Surveys (DHS, 2002) reveal that the percentage of childless women at age 40–49 years ranged from <2% (Malawi, Tanzania, Zambia) to 9% (Philippines), with a mean value close to 4%. Among married women, the rates are even lower, ranging from 1 to 8%, with a mean value of <3%. In some countries men were also surveyed: the percentage remaining childless at 45–59 years seems to be systematically lower than the percentage for women in African countries, but may be higher in other parts of the world.

The relatively low level of permanent infertility seen in the developing world refers to primary infertility (according to the demographic definition). The picture changes when one considers secondary infertility. In 14 of the 23 countries of sub-Saharan Africa that were studied, the percentage of couples with secondary infertility was >25%. In Zimbabwe, the percentage of women (aged 25–49 years) with secondary infertility was 62% (S.Rutstein and I.Shah, unpublished data). In other parts of the developing world, the prevalence of secondary infertility was also high, with countries such as Egypt, Turkey, Bolivia and Peru experiencing rates of between 15 and 20%, Bangladesh and Haiti between 20 and 25% and Cambodia, India, Indonesia and Nepal >25% (S.Rutstein and I.Shah, unpublished data).

The low primary infertility rates in developing countries may be due to marriage and pregnancy occurring at a younger age than in developed countries. The biggest factors leading to the high secondary infertility rates in these countries are sexually transmitted infections (STI) (see Table I) and medical interventions under unhygienic conditions, particularly post-partum.

One STI that deserves special consideration is HIV/AIDS. In 2001, an estimated 5 x 10^6 people became infected with HIV worldwide. Approximately 3.5 x 10^6 of these new infections occurred in sub-Saharan Africa, bringing to 28.5 x 10^6 the total number of people living with HIV/AIDS in that region (UNAIDS, 2002). The consequences of this epidemic are devastating, impacting not only on child and adult mortality rates and life expectancy, but also on the social, economic and demographic factors required for development. The overriding pre-occupation with the social and demographic consequences of the unprece-

Table I. Estimated prevalence and annual incidence of sexually transmitted infections excluding HIV by region (World Health Organization, 2001)

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<tr>
<th>Region</th>
<th>Population aged 15–49 years (x 10^6)</th>
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<th>Prevalence per 1000</th>
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<td>North Africa and Middle East</td>
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<td>Eastern Europe and central Asia</td>
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<td>Sub-Saharan Africa</td>
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<td>South and South</td>
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<td>New Zealand</td>
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<tr>
<td>Latin America and Caribbean</td>
<td>260</td>
<td>18.5</td>
<td>71</td>
<td>38</td>
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dent HIV/AIDS-induced mortality has drawn attention away from a less studied aspect of the epidemic, namely the links between HIV and fertility.

Evidence gathered from both clinical and population-based studies suggests that fertility is reduced in HIV-positive women. Analyses of data from a number of sub-Saharan African countries with high HIV prevalence indicate 25–40% lower fertility in women with HIV (Zaba and Gregson, 1998), several of these countries are experiencing population growth rates that are substantially lower than would have been expected in the absence of HIV/AIDS. Although some of this subfertility reflects prior exposure to other STI among HIV-positive patients, about half is thought to result directly from the infection itself.

The mechanisms causing lower fertility in women with HIV are not well understood, but probably reflect a combination of biological and socio-behavioural factors. For instance, adverse pregnancy outcomes (spontaneous abortion, stillbirths) have been reported to be more common in infected women, and the prevalence of amenorrhoea increases at the later stages of HIV infection. Other factors unrelated to decreased fecundability may include reduced coital frequency, desired family size and increased contraceptive use, including condom use (Nebie et al., 2001; Gregson et al., 2002).

All this points to a complex relationship between infertility and HIV/AIDS. It has been demonstrated, for example, that being infertile can lead to an increase in ‘risky’ sexual behaviour simply because one may want to ‘try out one’s potential’ with as many partners as possible. This is life-threatening in the current context of the AIDS epidemic in many developing countries.

To explore the link between infertility and the prevalence of HIV/AIDS and other STI, the levels of primary and secondary infertility in 28 developing countries participating in the Demographic and Health Surveys have been analysed and compared with HIV prevalence data (DHS, 2002; UNAIDS, 2002). At the population level, HIV prevalence was not significantly related to primary or secondary infertility. Prevalence of syphilis was related to prevalence of primary infertility and trends in HIV and other STI were related to trends in increasing secondary infertility.

Geographical correlations do not necessarily indicate causal relationships. On the whole, however, primary infertility is often low and stable in developing countries, whereas secondary infertility is high and rising due to the prevalence of STI and lack of quality reproductive health care. The AIDS epidemic is also a contributing factor to this trend, although more research needs to be conducted to determine its exact role.

Comparisons have also been made with infertility data from previous surveys. These use a similar methodology and set of questions including surveys from the World Fertility Survey Program (Vaessen, 1984), which were conducted prior to the onset of the HIV epidemic, in order to assess trends. For most countries with comparable data (Colombia, Haiti, Indonesia, Kenya, Peru, Philippines and Senegal), the percentage of women aged 25–49 years who were childless declined over time. However, countries most affected by HIV/AIDS, for example Kenya, Zambia and Zimbabwe, show a rising percentage of women in the 25–49 year age group reporting secondary infertility.

### Diverging trends in developed countries

In the developed world, permanent infertility tends to be significantly higher than in developing countries. One has to take into account, however, that infertility is used here in the demographic sense, not distinguishing between voluntary and involuntary infertility. Voluntary infertility has increased markedly since the 1970s in developed countries, whereas involuntary primary infertility in the sense of permanent sterility is about 3–5% in developed countries (Greenhall and Vessey, 1990). Nevertheless primary infertility (as defined in reproductive medicine), is probably becoming higher due to the increasing age at which women first attempt conception. Indeed, in contemporary populations of women who actively try to conceive, age-related decline of fertility is apparent. Data derived from the National Survey of Family Growth in the USA demonstrated that in 1995 the proportion of women who tried but did not succeed in conceiving their first child within 1 year, increased from 6% in the 15–24 year age group to > 30% in the 35–44 year age group.

In contrast to developing countries, the incidence of secondary infertility in the developed world is low due to more effective control of STI and the greater availability of reproductive health care.

Many developed countries experienced a baby boom in the 1950s and 1960s. One consequence was that, in these countries, the percentage of permanent childlessness in some cohorts reached low levels. Fertility and Family Surveys were conducted in a number of European countries from the late 1980s until the end of the 1990s. The proportion of permanently infertile women remained low in some countries (5–8% in Norway, Poland, Romania, Czech Republic, Ukraine), but was >10% in Finland, Sweden and in Canada and peaked at 18% in Switzerland. The proportions for men are usually higher, sometimes substantially; 17% in Finland, 21% in Switzerland (Fertility and Family Surveys, 1988–1999). These values are based on data collected in demographic surveys in which voluntary and involuntary infertility cannot be distinguished. The large differences between countries probably reflect large differences in voluntary infertility.

In The Netherlands, the mean age at which women deliver their first child has risen from 24.6 years in 1970 to 29.2 years in 2001. Both the large scale use of effective contraception and the growing popularity of ART have given the impression that fertility can be manipulated to one’s own preference. It is true that today fertility can be stopped temporarily using relative simple means; resumption of fertility, however, may be illusory, especially among women in their late thirties.

More detailed questions on the fecundity of respondents are often asked in demographic surveys. Self-evaluation of the ‘fertile’ status, however, often proves to be of poor quality. Data on difficulties to conceive may be of greater interest; indeed, many more women report that they had difficulties in becoming pregnant (and in delivering a live birth) than women having been unable to have a child. While these data must be handled with care as they are subjective assessments (Leridon, 1992), they do provide valuable information, particularly when time to conception (TTC) can be obtained (Baird et al., 1986): this seems feasible even in retrospective surveys. In France, the mean TTC for subfecund women aged 25–44 years during
the various causes of female infertility, clear limitations are still imposed by the age-related quality of the oocyte. Given the ever-increasing age at which women in the developed world are seeking to bear children, the search is on for new prognostic and therapeutic tools to enhance the chance of a successful ART outcome, including pronuclear scoring of the zygote, determining the cytoplasmic polarity of the oocyte, zona pellucida parameters, the degree of fragmentation of the polar body and embryo selection. Public debate on ethical, policy and public health issues will play an important part in redefining the limits our societies decide to place on access to available treatments for infertile women.

Current management of female factor infertility

Some 40–60% of infertility cases are attributable to female causes, which can be divided into several traditional categories (Insler and Lunenfeld, 1993). The mechanical causes of infertility (~40%), either congenital or acquired (for example, sequelae of STI), may be permanent (absent or irreversible pathology of the internal female genital organs), curable (by surgery), or able to be circumvented (by IVF). Endocrine causes, involving dysfunction of the hypothalamic–pituitary–ovarian axis, also represent ~40% (Insler and Lunenfeld, 1993). Advances in our understanding of endocrine mechanisms have led to the development of active principles with a progressively more precisely targeted action. Recombinant forms of various hormones essential for human reproduction (FSH, LH, hCG) are now available, making it possible to offer the female patient individualized treatment using pure and specific active principles.

More infrequent causes of female infertility are secondary to the presence of endometriosis or an immunological factor. Prognostic factors for increasing likelihood of female infertility include increasing age at first attempt at conception. Oocyte-related causes, sometimes of genetic origin, are increasingly regarded as linked to the age of the oocyte. This means that some infertility conditions of indeterminate origin are attributable to the social trend towards an increasing age of conception of the first child in European and American women.

In terms of surgical management of female infertility, laparoscopy has been a very efficient tool since it permitted simultaneous diagnostic and therapeutic procedures. The limits of surgery are apparent when there is bicornal tubal disease, severe tubal damage (e.g. thick hydrosalpinx, destruction/adhesions of the mucosa, frozen pelvis, ongoing genital infections), risk of tubal pregnancy and other associated severe infertility factors as well as other factors related to the global prognosis of the couple.

In other forms of treatment of female infertility, a number of decision-making tools are available. The Cochrane Database can serve as useful reference for clinicians in assessing therapeutic procedures such as IUI, and drug treatments such as gonadotrophins (Hughes et al., 2000a,b; O’Brien and Vandekerckhove, 2000).

While significant advances have been made in treating the various causes of female infertility, clear limitations are
cause of male infertility that has been identified is the presence of mutations in the androgen receptor gene. About 2–5% of cases of male infertility are due to congenital bilateral absence of the vas deferens and in most of these subjects one or two mutations in the cystic fibrosis transmembrane conductance receptor is also present, resulting in a form of atypical cystic fibrosis (CF) (Chillon et al., 1995). In these men it is mandatory to screen the female partner for CF mutations. If the female partner is a carrier of a CF mutation, appropriate measures have to be taken in order to prevent the birth of a CF child.

Each month, additional potential genetic mechanisms are identified in mice using the targeted disruptions of genes, and there is a need to determine if mutations in these genes are present in infertile men. One of the challenges facing andrologists is to determine the most cost-effective way of identifying genetic mechanisms given the increasing number of targets (Cram et al., 2001). At the moment, such an approach must utilize a logical evaluation on the basis of a thorough history and physical examination and the results of semen analyses and hormonal measurements.

New multi-centre study on ICSI

The Bertarelli Foundation’s Second Global Conference also addressed the lingering doubts on the safety of ICSI to mother and child (Wennerholm et al., 2002). A collaborative group from Sweden, Belgium and the USA presented the findings of a multi-centre study on the physical and psychological development of 5 year old children conceived in singleton pregnancies with the aid of ICSI. The aim of this prospective study was to investigate whether there is a difference in physical (health, growth and morphology) as well as psychomotor and psychological (cognitive, emotional and behavioural) development in pre-school singleton children born after ICSI compared with children born after spontaneous conception (SC).

In the medical part of the study, significant differences were found in rates of pre-term birth (< 37 weeks) and low birthweight (< 2500 g), both of which were significantly more common in ICSI children compared with spontaneously conceived (SC) children. Median birthweight was significantly lower in ICSI children (3317 g) compared with SC children (3420 g). Major malformations at the age of 5 years were more common in the ICSI group (7.0 versus 3.2%), probably due to selection bias at one centre. The results also indicated that there were no major differences in the general health and growth of ICSI children at the age of 5 years compared with SC children. In the psychological part of the study, no major differences were found between ICSI and SC children for emotional, behavioural, motor and cognitive development. For minor differences (visual–spatial) between ICSI and SC children, variables other than the conception mode could be responsible. Complete details of this study are available (Leslie et al., 2003).

Barriers to infertility treatment

Barriers to infertility treatment can be classified into three main categories: accessibility, economic cost, and cultural/societal factors. In developing countries, it is not unusual for all three to be present simultaneously, creating an almost insurmountable obstacle to adequate reproductive health care.

Based on case studies in the Gambia (Sundby, 1997) and Zimbabwe (Sundby and Jacobs, 2000; Runganga et al., 2001), barriers to general medical treatment include the lack of knowledge about where to go, poor infrastructure, shortage of public transportation and distance to the nearest clinic or hospital. The relationship between STI and infertility has been discussed above. In many developing countries, even STI preventive programmes face significant obstacles. Systematic approaches to the detection and treatment of STI in women have been able to capture approximately half of the infected patients, and many women do not seek care at all. Re-infection resulting from the lack of partner notification is common. Infertile women and men may not obtain, as a first approach, access to STI screening or drugs and even a simple clinical examination is sometimes omitted. Often only the woman is examined, because nobody asks for the partner, or he refuses to attend the clinic.

Concerning specific infertility management, access to more ‘advanced’ techniques, such as hormonal assays, sperm analysis, hysterosalpingography, or laparoscopic diagnosis is limited; furthermore, even if a diagnosis is made, ART is generally not available. Those patients in the Gambia and Zimbabwe who can afford to seek treatment must travel to the UK or South Africa and pay for private sector care if they want such treatments. For the majority of women, the cost of such treatments is out of reach and this inability to access infertility treatment has far-reaching social consequences. In many developing countries, women who are unable to bear children are rejected by their husbands and ostracized by society, often living as outcasts and perceived as inferior and useless.

There is a striking difference in the use of ART between developed and developing countries, as calculated by the number of treatment cycles divided by the number of women expected to require ART or in the number of cycles per 106 women (Table II). Israel has the highest IVF utilization rate. Denmark has the highest access to ART (in terms of number of ART cycles result-

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*a Adapted from Collins (2002).
ing in follicular aspiration) at 31.5%, Belgium reaches a rate of 18% and France, 15.8%. By contrast, access to ART in the USA is 4.3%, Argentina 1.9%, Brazil 0.7% and Mexico only 0.3% (World Health Report, 1998; Zegers-Hochschild et al., 2000). These values illustrate that while some developing countries may rapidly and efficiently acquire the latest technologies in infertility treatment, access remains available to only a few.

In developed countries, there are a number of reasons that might explain the lack of initiatives to facilitate greater access to ART. In many countries infertility is not considered a disease and is thus not covered by public or private health insurance. ART can be criticized on several fronts. For example, the lack of control in the quality of the service in most countries, including the high rate of multiple births, does not place infertility treatment in the best light. In Latin America, in particular, an important influential factor is the teaching of the Catholic Church, which strongly opposes ART and applies considerable moral pressure (‘Fertility is a gift from God, not a right of mankind’) on legislators and the public to prevent greater access to it. An extreme example of this approach is found in Costa Rica, where the Supreme Court has banned all forms of ART.

This is in stark contrast to a position paper by the World Health Organization (1994), which states: ‘Reproductive health is a state of complete physical and mental and social well being and not merely the absence of disease or infirmity, in all matters relating to the reproductive systems and its functions and processes. Reproductive health, therefore, implies that people are able to have a satisfying and safe sex life and that they have the capability to reproduce and the freedom to decide if, when and how often to do so.’ The Universal Declaration of Human Rights article 16.1, United Nations, 1948 also supports this view: ‘finally The European Convention on Human Rights, guarantees respect for family life and the right to found a family’ (European Convention on Human Rights and its Five Protocols, Articles 8 and 12).

Nevertheless, the decisive factor in preventing greater access to ART remains the high economic burden for fertile couples. Of the 93 ART centres reporting to the Latin American registry during 2000, only three are partially subsidized by their respective government. The rest constitute private hospitals or clinics that accept only those who can afford to pay the large fees.

In contrast to the 1970s, when Latin American scientists contributed significantly to the development of contraceptive methods such as copper intrauterine device, long-acting progestagens and Norplant (Pérez-Palacios and Garza-Flores, 1994), the medical profession today has failed to devise less expensive ways of performing ovarian stimulation, gamete handling and other procedures involved in ART without affecting success rates. During the 1970s, the major contributors to contraceptive development were non-profit organizations such as the World Health Organization and the Ford Foundation, which stipulated that investments in research and development had to be based on their acceptability and access by the developing world. A more serious commitment today to increasing access to better quality health care services, including infertility treatment, would be a major contribution to global solidarity and equity.

In the developed world, societal factors have resulted in a significant delay in childbearing and seeking access to infertility treatment (van Noord-Zaadstra et al., 1991; te Velde, 2002). The large number of women who have entered the workforce has transformed traditional notions of motherhood. The balancing act between a successful career and a family is a difficult one, and the typical consequence is postponement of childbearing to the age when fertility rates start to decline (typically after 31) (te Velde and Pearson, 2002). Women who seek to ‘have it all’ often harbour illusions about the ability of ART to compensate for the natural decline in fertility.

But even in the relatively prosperous developed countries, economic factors remain critical to determining access to infertility treatment. The number of countries where full reimbursement is available for multiple cycles is limited.

**Economic implications of infertility**

A number of analytical tools are available to measure the costs and benefits of infertility treatment. Full economic evaluations, which include costs, outcomes and a valid comparison, consist of four types: cost-effectiveness analysis, cost-minimization analysis, cost-benefit analysis, and cost-utility analysis.

Two cost-effectiveness studies, with incremental costs calculated from the study results (Goeree et al., 1993), have revealed a higher success rate of patients treated with IVF/ICSI versus patients on non-IVF standard therapy (for example, IUI with or without controlled ovarian stimulation). These costs were US$80 733 per pregnancy and US$63 785 (Goverde et al., 2000). A more recent study with an improved design and no treatment control group (Hughes et al., 2002) would have incremental IVF costs of only US$12 822 per pregnancy if the Goeree et al. costs were projected to 2002. A fourth study (Karande et al., 1999) showed a contrasting trend, with higher success rates of new patients on standard therapy versus IVF/ICSI, with incremental savings of US$14 088 for each pregnancy.

Based on these studies, one can conclude that IVF is more expensive than infertility drugs alone but is also more effective—provided that the patient group has already unsuccessfully tried the standard regime of infertility treatment. (Please note that these studies do not include patients with blocked tubes: most are concerned with IUI.)

Cost-effectiveness may be a valuable economic tool but it is not a sufficient reason for funding ART. Ultimately, society—in deciding which health care procedures should be publicly funded—sets priorities based on criteria other than cost-effectiveness. In Canada, the cost of all infertility treatments in 1995 was Can$450 ×10^6 (of which ~35% was for IVF or ICSI). Total Canadian health expenditures in 1995 were Can$74 ×10^9, which means that infertility treatments amounted to only 0.6% of the total. The annual cost of IVF/ICSI treatment in Canada would amount to Can$5.00 per capita (Collins et al., 1995a).

The direct costs of ART vary considerably from country to country, putting an unequal burden on couples that must pay for treatment ‘out of pocket’ (i.e. where expenses are not covered by public or private insurance). In Pakistan or Iran, the countries where IVF is the cheapest, treatment costs ~ US$1000 per cycle (Collins, 2002). In the USA, where it is the most expensive, a cycle costs on average US$10 000 (Collins, 2002). However, the apparent affordability of IVF in these developing nations is misleading. When one examines the costs of IVF as a ratio of gross...
Cost and availability of infertility treatment

The continuing challenge of multiple gestation

Any examination of the costs of IVF/ICSI must also consider the incidence of multiple births on these treatments, estimated as high as 32% for twins and 4.7% for triplets or higher order births (SART/ASRM, 2002), or as low as 23.9% for twins and 2.4% for triplets or higher order births (ESHRE, 2002). The direct costs of delivering and the consequent hospital stay for a single child in the USA in 1999 were estimated to be US$9000; the respective costs for twins, US$51 715; for triplets, US$149 598; and for quadruplets, US$247 482 (Callahan et al., 1994).

An examination of trends in the USA over the past 20 years shows a continuous rise in the number of twins, from 68 339 live births in 1980 (rate 18.9 per 1000 total births) to 118 916 live births in 2000 (rate 29.3 per 1000 total births) (National Vital Statistics, 2002). The percentage of twin gestations attributed to spontaneous occurrence in 1999 was 38.1% of the total (SART, CDC). Rates of multiple births per 1000 in countries as diverse as Finland, Australia, Israel and Japan also showed a marked increase between 1975 and 1995 (Imaiuzumi, 1998).

There are similar trends in high order multiple gestation (triplets and higher) in the USA, rising from 1.3 per 10⁵ live births in 1980 to 7.6 in 10⁵ in 1998, after which there was a slight levelling off (National Vital Statistics, 2002). Another source (CDC, 2000) calculates the rate of triplet and higher order multiple births by mothers’ age in the USA. In 1980, the mean number of multiple births for mothers of all ages was 37 per 10⁵ live births; in 1997, the mean increased to 173.6. The highest rate of multiple births (403.2 per 10⁵ in 1997) was seen in women aged 35–39 years. The rate of high order multiple gestations occurring spontaneously was 7.6 per 10⁴ in 1999 (SART, CDC).

High order multiple gestation is correlated with a higher incidence of severe prematurity and serious medical conditions. In the UK, low birthweight (<1500 g) was found in 0.7% of singletons, 9.0% of twins, 28.4% of triplets and 52.3% of quadruplets (UK Triplet Study, Botting et al., 1990). In Western Australia, the prevalence of cerebral palsy between 1980 and 1989 was about one among singletons per 1000 live births, nine among twins and 25 among triplets (Petterson et al., 1993).

While IVF and ICSI certainly bear part of the responsibility for the increasing number of high order multiple births, more attention should be focused on the relatively ‘low tech’ treatment of ovulation induction. While hard data are not yet available, there is reason to believe that uncontrolled, unregulated ovulation induction—often initiated by non-specialist physicians—makes up a greater proportion of higher order births than previously thought.

Psycho-emotional implications of multiple pregnancies for the family

The incidence of twin births in developed countries has risen steadily since the early 1980s, and this may be attributed to the increased use of ovulation induction and multiple embryo transfer in the treatment of infertility (Imaiuzumi, 1998). The 2000 Human Fertilization and Embryology Authority (HFEA) Annual Report showed 27.3% multiple births following IVF, 6.4% with donor insemination and 26.9% with micromanipulation (HFEA, 2000). Multiple pregnancy is associated not only with medical complications (for example, increased risk of preterm birth and low birthweight) but also with psycho-social stress (for example, the need for the parents to adjust to the prospect of a larger than expected family).

For the parents, the challenges of multiple gestation continue after birth. A survey of 576 mothers (Tamba Maternity Services Questionnaire 1998: unpublished data), showed that mothers of multiple children were more than twice as likely to suffer fatigue and depression. This level of emotional stress is captured in the following statement: ‘The children saw me crying with fatigue. Sometimes, I cannot stand up, physically or psychologically’ (Garel et al., 1997).

There is evidence that children born in multiples may lag behind singletons in development. Studies done on pre-term infants show that twins were less talkative, held and touched than singletons, and that maternal behaviour was predictive of cognitive development at 18 months (Ostfeld et al., 2000). At 4 years, another study on language development showed that twins were 6 months behind singletons, and one in three twins had a significant delay in development (Mittler, 1976). Behavioural problems in older siblings of twins were three times higher than among siblings of singletons with a 2–5 year age gap and six times higher in those with an 8–11 year gap (Hay et al., 1988). Physical disabilities such as cerebral palsy are also significantly more common in twins and triplets compared with singleton children (Petterson et al., 1993).

In general, the perinatal mortality rate is higher in twins compared with singleton children and higher still in children born as a result of ART treatment (HFEA, 2000), implying that more families with multiple births resulting from ART will suffer bereavement. Another difficult issue that some families will face is whether to reduce a higher multiple pregnancy to twins. Some parents may feel a lasting sense of grief and guilt associated with the death of one or more potentially healthy children.

In conclusion, there is an urgent need to address the issue of multiple births associated with ART. In addition, those caring for multiple birth children need to develop a better understanding of the needs and problems of those families who have more than one infant at the same time.

Emotional support during and after treatment

While much of the literature surrounding infertility treatment focuses on success rates and happy outcomes, there is still a...
substantial percentage in which even the most advanced techniques fail. The personal testimony of couples that will never be able to have a family of their own brings home the suffering of infertility, leaving an imprint of sorrow on patients’ lives.

Like any life crisis, those who have experienced it can best understand infertility, and since the 1980s, a number of self-help groups have been established both nationally and internationally. The effectiveness of such groups in fighting for the interests of their constituents can be seen in Australia, where the patient organization ACCESS Australia Infertility Network (Dill, 2002) succeeded in preventing the Government from withdrawing funding that has helped to bring >25 000 IVF babies into the world in the last 10 years (Dean and Sullivan, 2003).

Surrogacy is another area of infertility in which the emotional aspects have been inadequately researched. First-hand accounts of altruistic surrogacy reveal that it is a highly complex psychological process (Ryan, 2002). Despite a conscious decision to bear a child for another couple, the surrogate mother may be torn by strong emotional conflicts when giving the baby to the intended parents. A sense of personal loss and grief may persist for some time afterwards. Complicating matters further, the legal status of children born from surrogacy is not always clearly defined, as demonstrated by a number of highly publicized court cases.

Reproductive health policy issues

In industrialized countries, health policy issues at the top of the agenda differ widely. The revolutionary changes in human reproduction have triggered the need, not only for a wide ethical debate, but also for some form of regulation and control in three main areas:

- **The technical excellence of the services rendered.**
  Regulations to avoid abuse, prevent possible damage to the mother and the child, and outlaw techniques unacceptable in a couple’s given cultural setting, including mechanisms to ensure adherence to ethical and good medical practice guidelines.

- **A monitoring system to control all practitioners and their premises.**
  An important mechanism to ensure that infertility services are practised to the highest standards is the provision of national guidelines provided by medical societies or ministries of health (Royal College of Obstetricians and Gynaecologists, 2002). Such guidelines, whether voluntary or statutory, protect patients and practitioners by providing them with clear terms of reference (Cohen and Jones, 2000).

  In the UK, for example, in 1990 Parliament voted into law the Human Fertilisation and Embryology Act, which established the HFEA. The HFEA was created to regulate and license clinics conducting any infertility treatment involving the use and creation of embryos outside the body, any treatment involving the use of donated gametes, the storage of any gametes or embryos and research on human embryos. The HFEA was also given the important function of maintaining registers of information about donors, treatments and children born as a result of those treatments (Brinsden, 1993).

  An integral part of monitoring is the establishment of national and international ART registers to which all centres conducting ART should be required to submit treatment and outcome data. This is an excellent way to make results transparent and enable prospective users to choose the best centre.

  There are several European registers, for example, FIVNAT (France), the Deutsches IVF Register (Germany) and the HFEA register (UK). In most cases, however, external auditing is lacking and therefore their accuracy and completeness may be questionable. There is growing momentum for national and regional registries on ART. In many countries, this is still voluntary, but Germany and Belgium are leading the way in making this procedure mandatory.

International registers

Since ART centres have been established in all industrialized countries, an International Working Group for Registers of Assisted Reproduction was established in 1991. The first results were presented the same year in Paris; thereafter, biannual reports have been published (Cohen, 2001). Data on ART in Europe, drawn from national registers, are collated and published by the ESHRE. The most recent report, covering cycles initiated in 1999, appeared in December 2002 (Nygren and Andersen, 2002).

In the USA, similar data are published by the Society for Assisted Reproductive Technology (SART) and the American Society for Reproductive Medicine (ASRM) (SART/ASRM, 2002). A bill has been proposed by Senator Ron Wyden to establish a national registry at the Centers for Disease Control (CDC).

Since 1990, the Latin American Registry on Assisted Reproduction (RLA) (Zegers-Hochschild et al., 2000) has published annually a regional registry, which includes >90% of all procedures performed from Mexico in the North to Chile in the South. The most recent report includes procedures initiated during 2001 and babies born up to September 2002.

Conclusions

The word infertility is often used in a vague, abstract sense. It is important to define exactly what is meant by this term and related concepts. In the developed world, the main issue is primary infertility, which continues to rise as the population ages and the mean age of childbearing increases. In the developing world, high rates of secondary infertility—typically caused by STI and post-partum complications—is the main issue. The impact of the HIV/AIDS epidemic on fertility needs further exploration.

There are a number of barriers that prevent infertile couples from gaining access to treatment. One of the most important is economic. In most countries, these relatively expensive procedures—amounting to 25% of average annual income in the USA—must be financed out of pocket. In many of the poorest countries, these procedures are too expensive for all but a privileged few. The role of culture and social barriers to infertility treatment should not be underestimated. Catholic religious authorities, for example, forbid the use of certain ART procedures. In many countries, infertility is still taboo.
The management of infertility has made great strides in the past decades. IVF has become a standard therapy for female mechanical and unexplained infertility and ICSI for male factor infertility. Nevertheless, the use of these assisted reproductive technologies should not be seen as a substitute for the proven medical approach of a thorough examination and individual diagnosis.

Multiple gestation remains one of the most difficult issues to solve in infertility treatment. While current IVF practices are often blamed, more attention needs to be focused on hyperstimulation in ovulation induction. Whatever the origin, the goal should be the same: reducing the numbers of twins, triplets and higher orders of multiple births. National ART guidelines, such as those of the Royal College of Obstetricians and Gynaecologists in the UK, are becoming more widespread. National registries of infertility treatments for each patient, both on a voluntary and mandatory basis, are also growing. Both of these trends offer considerable promise in curbing excesses that may offer better success rates for individual cycles of treatment but unacceptably high costs for society as a whole.

References

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