Assisted reproduction in developing countries—facing up to the issues

For millions of couples around the world, the inability to have children is a personal tragedy. For a significant proportion of them, the private agony is compounded by a social stigma, which can have serious and far-reaching consequences. It is not surprising therefore that the demand for assisted reproductive technologies (ART) is growing in all regions. But how can the provision of these technologies—which are expensive and have a success rate of less than 30%—be justified in developing countries with poorly developed health services that are still struggling with infectious and chronic diseases, such as tuberculosis, malaria and HIV/AIDS?

In 2001, the World Health Organization convened a meeting on "Medical, Ethical and Social Aspects of Assisted Reproduction", to examine a number of issues surrounding the treatment of infertility, and to learn about country and regional experiences with assisted reproduction. Specifically, the objectives of the meeting were (i) to review and assess recent developments in ART, (ii) to identify unresolved issues in the field, and (iii) to provide recommendations for future research.

This issue of Progress looks at some of the topics that were covered at the meeting, starting with an overview of the situation in developing countries, where infertility rates are high and private ART services are being set up in response to the needs and demands of individuals. This is followed by a series of short reports from several regions and countries on the current status of ART services.

Attitudes to assisted reproduction are very much influenced by the specific cultural and social context. Manipulation of sperm, oocytes and embryos raises numerous questions to which there are no easy answers, and which often arouse strong emotions. The article on page 5 outlines some of the ethical and legal issues surrounding the use of ART, which need to be discussed openly by all involved parties wherever such services are made available.

In the 25 years since the birth of the first baby resulting from in vitro fertilization, there have been tremendous advances in scientific techniques and medical applications of ART. But there are still areas where more research is needed. For instance, concerns have been expressed about the long-term development of the child. Experience in this area is, of necessity, rather limited, especially for the newer techniques, but the results so far are reassuring. As noted in the article on page 6, however, continued vigilance is needed to monitor the long-term outcomes of ART.

As part of this monitoring effort, and as ART becomes available in more and more countries, national and international surveillance systems assume considerable importance. The article on page 7 describes some of the difficulties in ensuring that such systems produce reliable and comparable data. Box 3 (The Latin American Registry of Assisted Reproduction) on page 7 describes an attempt in Latin America to ensure standardized reporting from ART centres in a number of countries.
ART in developing countries—
a response to individual need or a social
priority?

There are over 186 million couples in
developing countries alone (excluding China) today who are affected by
infertility (both primary and second-
ary). Rates of infertility vary consider-
ably from country to country; in the
worst-affected areas, over 25% of
couples may be unable to have chil-
dren. Most of the infertility in develop-
ing countries is attributable to dam-
age caused by infections of the repro-
ductive tract, notably gonorrhoea and
chlamydial infection.

In addition to the personal grief and
suffering it causes, the inability to
have children—especially in poor
communities—can create broader
problems, particularly for the woman,
in terms of social stigma, economic
hardship, social isolation, and even
violence. Various studies have found
that childless women in developing
countries are often abandoned by their
husband, subjected to violence, or
treated as servants by the husband’s
family. In some societies, mother-
hood is the only way for women to
improve their status within the family
and the community. On a practical
level, many families in developing
countries depend on children for eco-
nomic survival. While many people,
therefore, would not consider infertil-
ity a disease in itself, it can certainly
be said to be a social and public
health issue as well as an individual
problem.

It is not surprising, therefore, that
there is a growing demand for serv-
ices that can help infertile couples to
conceive. In practice, this means
ART—artificial insemination, in vitro
fertilization, gamete or zygote
intrafallopian transfer, intracytoplas-
mic sperm injection, embryo freezing
and donation, and surrogate mother-
hood (see Box 1 on page 3). The fact
that these services are expensive
and controversial has not prevented
their appearance in developing coun-
tries.

This inevitably raises questions about
whether such services are justifiable
in a context where health resources
are severely limited, where there are
other pressing public health problems
that are not adequately addressed,
and where national goals may include
reducing fertility rates in the popula-
tion. In addition, it is argued that
resources would be better spent on
tackling the causes of much of the
infertility—the reproductive tract in-
fektion which are not diagnosed or
adequately treated.

Whatever the merits of the various
arguments, it has to be recognized
that couples who want children will go
to great lengths to have them, and
that there will always be providers to
make services available to those who
can pay for them. Thus, while ART is
still not easily accessible in develop-
ing countries—and is extremely ex-
pensive—it is starting to make an
appearance. Governments in these
countries therefore have a responsi-
ability to ensure that the services pro-
vided—whether in the public or the
private sector—are safe and effec-
tive. The majority of developing coun-
tries where ART is available have not
formally addressed these issues, al-
though some are considering or using
approaches based on those used in
developed countries, including legis-
lation, management guidelines, li-
censing, and reporting systems. Oth-
ers have approached WHO for ad-
vice on how to handle the introduction
of ART.

The lack of appropriate guidelines
and regulations in most developing
countries is a serious drawback in
efforts to improve the quality of the
services provided. In the absence
of national legislation, health profes-
sionals are challenged to implement some
form of self-regulation, giving some
form of recognition to practitioners
who are qualified to perform the pro-
cedures and have access to adequate
facilities. Centres should be encour-
gaged to standardize procedures and
equipment and to share their results
and expertise in a genuine collabora-
tive effort aimed at raising profes-
sional standards and avoiding mis-
use of the technologies.
Regional and country perspectives

The view that the provision of ART services is inappropriate in developing countries takes no account of the great heterogeneity of the developing world. Countries classified as “developing” vary enormously in their level and pace of development, as well as in their cultural, moral and religious values. Some countries already have the laboratory facilities and personnel to deliver sophisticated medical services, as well as an emerging middle class that has the financial capacity to pay for such services. On the other hand, in a number of countries, strong religious opposition to ART on ethical grounds has meant that there has been little or no development of services. The WHO meeting on assisted reproduction heard reports on the current situation in a number of developing regions and countries.

**India**

There is a huge stigma attached to childlessness in Indian society, particularly for the woman, and couples who can afford to do so will go to great lengths to obtain treatment for their infertility. Anjali Widge of the Population Council, New Delhi, reported that, in 1999, there were about 60 centres offering ART in India, almost all in the private sector. An evaluation of the few existing public sector centres is currently being considered, with the expectation that it may lead to their strengthening. There is, unfortunately, no monitoring or regulation of ART centres, and little discussion of the moral, ethical and social issues raised by the technologies. The first case of surrogate motherhood in the country in 1997 brought to the fore the need

**Box 1. Explanation of terms**

**Assisted reproductive technology**—any treatment or procedure that involves the in vitro handling of human oocytes and sperm or embryos for the purpose of establishing a pregnancy.

**Embryo donation**—the transfer of an embryo resulting from an oocyte and sperm that did not originate from the recipient or her partner.

**Embryo transfer**—procedure in which one or more embryos are placed in the uterus or fallopian tube.

**Gamete intrafallopian transfer**—a procedure in which oocytes and sperm are transferred to the fallopian tubes.

**Intracytoplasmic sperm injection (ICSI)**—an IVF procedure in which a single sperm is injected into an oocyte.

**In vitro fertilization (IVF)**—fertilization of an oocyte outside the body.

**Preimplantation genetic diagnosis (PGD)**—screening of cells from preimplantation embryos before transfer, for the detection of genetic or chromosomal disorders.

**Surrogate mother**—a woman who carries a pregnancy resulting from third-party oocytes and sperm, with the intention or agreement that the offspring will be brought up by one or both of the individuals who produced the oocytes and sperm.

**Zygote intrafallopian transfer**—a procedure in which a zygote (a fertilized oocyte) is transferred to the fallopian tube.

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It has to be recognized that couples who want children will go to great lengths to have them, and that there will always be providers to make services available to those who can pay for them.
In Latin America, ART is generally not provided in public hospitals, and the poor have no access to these services. This has engendered a feeling of discrimination and resentment.

**Box 2. Facts about ART**

- About one million children have been born as a result of ART. (This number does not include babies conceived with artificial insemination.)
- Success rates in developed countries are generally around 25% (in terms of live births per cycle) in women under 34 years of age. However, rates differ immensely between countries, partly because of differences in skill levels, but principally because of differences in techniques.
- The rates of spontaneous abortion are heavily age-dependent, but the average is around 18% of pregnancies, which is not higher than the rate for spontaneous abortions in natural conceptions.
- Most countries today report an ectopic pregnancy rate of 1–2%, which is not significantly higher than the rate in the population as a whole. In the early days of ART, higher rates were reported, reflecting the fact that most women undergoing the procedure some years ago had tubal damage.
- Multiple pregnancy rates vary considerably: the USA reports a rate of 37% while the rate for Europe is around 29%.

for clear ethical guidelines on ART; such guidelines have recently been developed by the Indian Council of Medical Research, although they have not yet been implemented.

**Latin America**

Florence Luna, from the University of Buenos Aires, Argentina, reported on the situation in Latin America. Stressing that the countries of the region are in fact very diverse, she noted nevertheless the widespread influence of the Catholic Church, and the large gaps in most of the countries between the rich and the poor. In general, ART is not provided in public hospitals, and the poor generally have no access to these services. This has engendered a feeling of discrimination and resentment, especially in countries, such as Argentina, that have a tradition of strong public health systems.

Very few countries in the region have legislation or formal regulations on ART. In some cases, legislation is deliberately not sought because of a fear that it would be overly restrictive, given the influence of the Catholic Church. There appears, however, to be a scientific consensus that ART should be provided only to infertile, heterosexual couples, and that every cryopreservation programme should be linked to a programme of donation or adoption of embryos. These issues are, in fact, highly controversial, but there is surprisingly little dialogue between the various concerned parties.

**Middle East**

Prevention and treatment of infertility are of particular significance in the Middle East, because a woman’s social status, dignity and self-esteem are closely related to her ability to have children. It might therefore be expected that ART would have been welcomed in the area. However, as noted by Gamal Serour of the International Islamic Center for Population Studies and Research, Cairo, Egypt, the techniques raise various religious and cultural issues, and it was not until the mid-1980s that ART centres started to be established in the region. One of the stumbling-blocks to acceptance of the techniques was the unacceptability to the main religious groups of the involvement of a third party in the act of procreation. Thus, in most countries of the region nowadays, artificial insemination using the husband’s sperm is allowed, but not techniques that use gametes from outside the couple. Another factor delaying the establishment of ART centres was their cost. Most centres are in the private sector and the cost to the patient is still quite high in relation to average income.

**Sub-Saharan Africa**

Having children is generally considered the main purpose of marriage in Africa, and the inability to have children remains a major cause of divorce. At the same time, the incidence of infertility in many countries of the region is high, for a number of reasons. Much of the infertility is the result of genital infection, which may have been sexually transmitted, or caused by traditional practices, such as female genital mutilation, or by undergoing gynaecological interventions in unhygienic conditions. There is thus a potentially large demand for ART services. Osato Giwa-Osagie of the University of Lagos, Nigeria, and Godfrey Tangwa of the University of Yaoundé, Cameroon, gave an overview of the situation in the English- and French-speaking countries of the region, respectively.

The concepts of artificial insemination, in vitro fertilization and gamete donation are generally well accepted in Africa. The first baby born in West Africa as a result of IVF was delivered at the Lagos University Teaching Hospital in 1989. By 2001, there were eight assisted conception centres carrying out IVF in sub-Saharan Africa, as well as numerous other centres offering artificial insemination. However, the providers of these services currently operate in a sort of legal and ethical vacuum, since there is virtually no state regulation of ART. There is a need for greater inter-country collaboration within the region, to develop regulatory approaches that respond to the specific African context.
The advent of IVF in the 1970s sparked intense debate about the use of ART and the social and legal implications it was predicted to have. Many of the ethical questions raised then are still debated today, and with each innovation in the technology a new dimension is added to the debate.

ART—whether it is fairly simple artificial insemination or intracytoplasmic sperm injection—separates reproduction from sexual intercourse, but still involves a man and a woman. In addition, in IVF and related techniques, fertilization takes place outside the body, which means that gametes and embryos are potentially available for testing, manipulation and research. For these reasons, some people reject ART as intrinsically morally unacceptable. Such objections are typically based on either religious belief or traditional assumptions about the nature of relationships and the role of the family.

Even those who accept the idea of in vitro fertilization as treatment for an infertile heterosexual couple in a stable relationship might have reservations about making such treatment available to other individuals—e.g. single women, postmenopausal women, or homosexual couples. Indeed, in many countries, such people are excluded from receiving ART services. The objections are often based on preconceived ideas of what should constitute a family unit. However, the reality in many countries is that families vary enormously in their composition, and there is no convincing evidence that children from conventional families do significantly better than others. Thus the ethical basis for restricting the availability of ART in this way is tenuous.

The techniques themselves raise a number of problematic issues. For example, when embryos are formed outside the body, what can be done with those that are not transferred? Is it acceptable to use them for research? Could they be donated to another infertile couple? Should they be frozen for future use? Or should they be destroyed? And who has the right to make these decisions—the providers of the oocyte and sperm, the medical profession, or the policy-makers?

These and similar questions are becoming even more urgent as preimplantation genetic diagnosis (PGD) becomes more common. Embryos can now be screened in vitro for a wide range of genetic disorders, and those found to be affected discarded. PGD also makes it possible to select the sex of the offspring. While most people would accept this as a way of avoiding the transmission of serious sex-linked impairments, many would regard it as ethically unacceptable if done simply for parental preference. Nevertheless, it is acknowledged that, in some countries, sex selection in this manner takes place.

Other tricky ethical questions concern the practice of transferring several embryos in order to increase the likelihood of pregnancy. If all the embryos successfully implant, the woman faces the prospect of a high-order multiple pregnancy, with its attendant increased risks of obstetric complications, premature birth and disability. In some countries in these circumstances, it is common practice to destroy one or more of the fetuses in order to increase the chances of survival of the others.

In many countries, questions of parentage and legitimacy of children born as a result of ART involving a donor are unresolved. Indeed, many couples who have had a child as a result of ART would prefer to keep it secret, and may not even tell the child.

These and many other issues raised by in vitro fertilization, and particularly by the use of donor gametes, are aggravated by the lack of public policies to regulate ART. As a result, individual doctors often have broad administrative discretion in individual care, and the more general ethical, social and legal issues are not widely debated. As the techniques become
more widely available, however, the questions will need to be resolved.

It is vitally important that the general public be closely involved in all aspects of the debate. Infertile couples need to be aware of the social, ethical and medical issues surrounding their decision to undergo ART, so that they can make truly informed choices. Local and national patient support groups can play a key role in fostering dialogue and advocating for improved patient management.

Long-term effects of ART—the physical and psychological development of the child

It is already 25 years since the first human baby resulting from in vitro fertilization (IVF) was born. At the time, the event was a widely publicized, celebrated, and controversial landmark. Since then, IVF has become routine and widely accepted, and is now only one of a number of potential treatments for infertility. Since 1978, more than one million babies have been born as a result of IVF, and it has been estimated that, in some European countries, up to 5% of all births are now a result of ART.

One concern that has been expressed since the early days of assisted reproduction is that the children will be somehow “disadvantaged”, physically or psychologically, by the process of their conception. One apparent difference is the higher incidence of multiple births following IVF, and the resulting higher proportion of preterm and low-birth-weight infants. However, allowing for these factors, the evidence so far indicates no difference in physical health between children conceived using ART and those conceived naturally.

The psychological development of children born as a result of ART has also received considerable attention. It has, for instance, been suggested that the stress associated with the experience of infertility and its treatment may result in parenting difficulties when a child is eventually born. Or that the parents may be overprotective, or have unrealistic expectations either of their children or of themselves as parents.

A recent review of research on parenting and the psychological development of children concluded that, from the evidence available so far, such concerns are unfounded. Parents of children conceived by ART appear to have good relationships with their children, and there is no evidence of cognitive impairment in singleton children born at full term. Nevertheless, experience so far is limited. Most studies have included only children before adolescence, and the quality of the studies has been variable. Samples are often small, unrepresentative and poorly defined, and without appropriate controls. In addition, for some types of ART, such as surrogacy and embryo donation, very little is known about the children’s development.

Thus, while existing knowledge does not give rise to specific concerns, many questions remain unanswered, particularly in relation to the newer technologies. ICSI, for example, in which a single sperm is injected directly into an egg, is a relatively recent technique that has provoked considerable debate. First used about 10 years ago, the technique was developed essentially through its clinical application in humans, and experiences in animal studies are very limited and possibly not relevant to humans. ICSI is used essentially in the treatment of male infertility, and concerns have been raised about the potential use of abnormal sperm, the bypassing of the usual process of natural selection, and the possibility of damaging the egg or embryo, all of which may produce changes in genetic material. While the evidence on the short-term health of ICSI offspring is reassuring, the WHO meeting noted that further research was needed on a variety of aspects, and recommended that the risk of congenital malformations in such children should continue to be monitored.

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Concerns about the safety and efficacy of ART have led a number of countries to set up monitoring or surveillance schemes to provide information for policy-makers, health care professionals and consumers. However, there is significant variation between countries in both the quantity and the quality of the data available, as well as in the definitions used.

At the national level, there are two basic options for collecting data. The first is to ask each clinic in the country to prepare an annual report covering items specified by the national registration body. This is the approach used in Scandinavian countries, for example. The second option is to collect data for each cycle individually, preferably in a direct system, where details are reported before the outcome of the treatment is known. This system is more complicated and expensive, but provides more reliable data, and is used in Germany and the United Kingdom, among others. Ideally, national data should be published once a year.

There are currently four regional bodies, which collect the national reports and produce their own annual regional reports. These bodies cover Australia and New Zealand, Canada and the USA, Europe and Latin America (see Box 3). Regional bodies are currently being formed in South-East Asia. At global level, the International Working Group for Registers on Assisted Reproduction is a task force under the International Federation of Fertility Societies (IFFS), and has so far produced five world reports, the most recent in 2001.

Ideally, each country should report the results of direct treatment (e.g. pregnancy rates), pregnancy outcome, child development and side-effects of treatment for the women. Most registries today deal with only the first category, covering the proportion of pregnancies, abortions, ectopic pregnancies, and deliveries relative to started cycles, ovum pick-up rates and embryo transfers. One area of considerable confusion is the definitions used for the various statistics reported. For instance, in reporting success rates, different numerators and denominators have been used. The numerator may be the number of pregnancies or the number of live births. But even once that decision is made, questions arise as to how to define pregnancy—whether as the presence of a gestational sac or a positive pregnancy test. The concept of live birth is reasonably straight-forward.

Box 3.
The Latin American Registry of Assisted Reproduction

ART is available in almost all the countries of Latin America, mostly in private institutions. However, because of the lack of national regulatory bodies and a general reluctance to deal with controversial issues, in the early days very little was known about the number and type of procedures performed in each country.

In 1990, a multinational registry of assisted reproduction (Registro Latinamericano de Reproducción Asistida) was initiated, with three objectives:
1. to create an educational tool that would allow consumers to evaluate the costs and benefits of ART procedures;
2. to develop a comprehensive regional database to serve as an external reference for each centre’s self-evaluation;
3. to develop a robust database that could be used for epidemiological research.

The registry currently covers 93 centres in 11 countries, and collects the following information:

- number of initiated cycles, follicular aspirations and transfer cycles;
- pregnancy, delivery and live-birth rates by follicular aspiration and by transfer cycles;
- pregnancy, implantation and multiple gestation rates according to the age of the woman, number of transferred embryos and stage of development at time of transfer;
- outcome of clinical pregnancies, i.e. abortion, ectopic pregnancy, stillbirth, live birth, neonatal death;
- gestational age at delivery, birth weight, major malformations, and cytogenetic analysis of abortion material.

The centres provide their data to the registry using a standard software. Results are reported and published as summaries for Latin America as a whole, and results of individual clinics are not disclosed. Over the years, the registry has served as an educational instrument for the centres performing ART. Its activities have also expanded to include continuous education and multinational research.

The activities of the ART community in Latin America are described on the web site <www.rediara.com>.
forward, but simply measuring live births does not give any indication of the health status of the infant.

As for the denominator, this is complicated by the fact that ART is not a single procedure carried out at a particular point in time. It is rather a cycle of treatment, beginning typically with ovarian stimulation, ovum retrieval, fertilization, and embryo transfer. A cycle may be discontinued at any of these steps, for clinical reasons, because of medical complications, or simply because the couple decides to withdraw from treatment. Rates have been reported relative to the number of cycles or the number of cycles commenced, which obviously give very different success rates.

Even a standardized way of presenting results can be misleading, if used to compare the performance of different centres. Success rate is greatly influenced by the selection of clients—rates are higher in younger women—and by the procedure used. Ovarian hyperstimulation and transfer of more than one embryo have a higher success rate but also a higher risk of multiple pregnancy.

The reporting of outcome of delivery is generally much more difficult to organize at national level. Thus, monitoring of birth outcome is usually done by individual clinics. One exception is the Scandinavian countries, where national birth registers can be cross-linked to specific ART registers, allowing the compilation of complete information.

Follow-up of the child through adolescence to adulthood is also needed to monitor physical, mental and psychosocial development. Data collection in this case is even more cumbersome, and is generally only done for small samples of individuals. Reports in this category are still scarce, and more information is urgently needed if the long-term safety of the various ART procedures is to be unequivocally demonstrated.

**Success rate is greatly influenced by the selection of clients—rates are higher in younger women—and by the procedure used.**

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**New Publication**

**Towards adulthood: exploring the sexual and reproductive health of adolescents in South Asia**

Edited by: Sarah Bott, Shireen Jejeebhoy, Iqbal Shah and Chander Puri

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This publication provides a comprehensive overview of the socio-demographic and sexual and reproductive health situation of adolescents in South Asia, including available evidence about the health risks and challenges that young people face in South Asian countries. The chapters in this volume are detailed summaries of papers and panel discussions from an international conference entitled “Adolescent Reproductive Health: Evidence and Programme Implications for South Asia”, held in November 2000 in Mumbai, India. The volume covers a wide range of issues, including: factors that undermine adolescents’ ability to make informed sexual and reproductive choices; the social context and health consequences of early marriage and childbearing; the sexual behaviour and attitudes of adolescents before marriage; sexual coercion against young people; the extent to which adolescents take measures to protect themselves from unwanted pregnancy and sexually transmitted infections; abortion among married and unmarried adolescents; the physiological, behavioural and social risk factors surrounding STIs/HIV among adolescents; communication between adolescents and adults; and the extent to which family relationships can be dominated by fear and violence. Drawing on the extensive and diverse evidence presented, wide-ranging policy and programme recommendations are suggested.