Foreword

The last quarter of the 20th century has witnessed several major advances in reproductive medicine. One of the most widely publicised, celebrated and, at the time, controversial medical landmarks in this area was the birth, in 1978, of the first human baby resulting from *in vitro* fertilization (IVF). Since then, IVF has become a routine and widely accepted treatment for infertility. However, IVF is but one of many procedures in the increasingly complex and sophisticated field of biomedicine known as assisted reproduction. Since 1978, nearly one million babies have been born worldwide as the result of assisted reproductive technology (ART) of one form or another. It has been estimated that in some European countries up to five per cent of all births are now due to ART. It is clear that ART has made a significant impact on the lives of many infertile and subfertile couples. However, it has also been the source of great disappointment to those couples for whom ART has proven unsuccessful and to many more infertile people around the world who have no access to these technologies.

It is commonly accepted that infertility affects more than 80 million people worldwide. In general, one in ten couples experiences primary or secondary infertility, but infertility rates vary amongst countries from less than 5% to more than 30%. Most of those who suffer from infertility live in developing countries where infertility services in general, and ART in particular, are not available. Malaria, tuberculosis and infection with the human immunodeficiency virus (HIV) among other diseases which have significant morbidity and mortality and adversely affect developing country economies, are, justifiably, the centre of public health attention. In many developing countries, infertility is the result of genital tract infection which includes sexually transmitted infections (STIs), postpartum or postabortal infection and pelvic tuberculosis or schistosomiasis. Tubal blockage is responsible for infertility in up to two-thirds of infertile nulliparous women in sub-Saharan Africa and between one-quarter and one-third of infertile women in developed and developing countries, respectively. It is often argued that the solution to the problem of infertility in developing countries can only be found in prevention of infertility through prevention of STIs and unsafe abortion. Therefore, the use of ART to manage infertility is a contested issue in the context of the cause of the problem, the attitude to overpopulation and the availability of scarce health resources in developing countries. Even in developed countries, however, where infertility patients stand a better chance of receiving infertility treatment, access to ART is limited. The generally high cost of ART procedures and national policies regarding accessibility and reimbursement leave many infertile people without the option of treatment.

Although infertility may not be a public health priority in many countries, it is a central issue in the lives of the individuals who suffer from it. It is a source of social and psychological suffering for both men and women and can place great pressures on the relationship within the couple. While the role and status of women in society should not be defined solely by their reproductive capacity, in some societies womanhood is defined through motherhood. In these situations, the personal suffering of the infertile woman is exacerbated and can lead to unstable marriage, domestic violence, stigmatization and even ostracism. Although peer and social pressures to have children vary from country to country, what remains common in all is the desperate need of infertile people to give birth to a healthy child. Many infertility consumer groups consider this to be a human right based on the following note from the UN Declaration of Human Rights, Article 16.1:

> Men and women of full age, without any limitation due to race, nationality or religion, have the right to marry and to found a family.

In the past decade, developments in the field of ART have intensified the hopes and the wishes of infertile people to resolve their infertility and have resulted in an increasing demand for such services in both developed and developing countries. While developments in ART have evolved rapidly, so have the ethical, social and political controversies which surround nearly all aspects of ART. Few other areas in medicine have posed so many social and ethical questions and have attracted so much public attention as ART.

International concerns about ART and its social and ethical implications were raised at the 52nd World Health Assembly in 1999, which requested the World Health Organization (WHO) to review recent developments in the field of ART as well as their social and ethical implications. In response to this request, the WHO Department of Reproductive Health and Research convened a meeting on the medical, ethical and social aspects of assisted reproduction on 17–21 September 2001.

WHO had previously dealt with the issue of ART in the context of other work on the subject of infertility. In 1990, a similar meeting was convened by WHO which resulted in a technical report entitled *Recent advances in medically assisted conception* (Technical Report Series No. 820, 1992). At that time, the emphasis was on technical aspects of ART. The meeting in September 2001 was organized to provide a forum for interdisciplinary discussion involving as many interested parties as possible. More than 40 participants from 22 countries took part in the meeting; they included clinicians, embryologists, social scientists, ethicists and consumer representatives. The objectives of the meeting were (a) to review and assess recent developments in ART; (b) to identify unresolved issues in the field; and (c) to provide recommendations for future research.

To permit in-depth analysis and discussion, the meeting did not cover the whole field of ART. Instead, it focused on a selected number of topics that either were too recent in their development to have been discussed at the previous WHO meeting in this area, or considered to present particularly difficult and pressing problems at the present time. These topics included national and international surveillance of ART, intracytoplasmic sperm injection (ICSI), manipulation and cryopreservation of gametes, multiple pregnancy, techniques of ovarian stimulation, preimplantation genetic diagnosis, psychosocial issues, ethical aspects in relation to the individual, to the couple and to the offspring, as well as issues of equitable access, the role of consumers and the place of ART in developing countries. The issue of cloning was not reviewed and discussed as it has been the subject of previous meetings held by WHO. Also, artificial insemination was not considered since it was covered in-depth by the *WHO Technical Report* published in 1992 and an update was not deemed necessary.

Background papers were commissioned from invited speakers and peer-reviewed prior to the meeting. The papers were briefly presented with emphasis being given to discussion and the delineation of recommendations for practice and future research. All of the meeting sessions were plenary to allow full interaction among the different disciplines. A wide variety of views and approaches was presented in an intense, dynamic and rich debate.

This publication comprises 6 sections, consisting of the background papers and the recommendations agreed to by the meeting participants. The papers are grouped by subject in an order similar to that of the meeting programme but also in a way that the different views are juxtaposed or complementary. Despite the diverse opinions on ART voiced at the meeting, there were many points upon which consensus was reached. These are reflected in the corresponding sets of recommendations, which appear in the last section of this report. These recommendations include some that are directed towards those responsible for health policy, some for those who are concerned with clinical practice and some to the research community. The meeting also agreed on a list of working definitions for ART for the purposes of the meeting's discussions. These definitions are included as a glossary in the report for consistency and clarity. However, it needs to be emphasized that these are not definitions that have been adopted by WHO, but they can be used to facilitate the standardization of language in the field and in national and international registries.

Over the past years, WHO has received several requests from developing countries for advice on how to handle the introduction of ART in their, often resource-poor, settings. On the other hand, the number of ART clinics in such settings is increasing and infertility consumer groups have become an established and outspoken force in several developing

countries. At the same time, there has been considerable international debate on related topics such as stem cell research, claims for successful human cloning and vigorous condemnations thereof. Inevitably, ART has ramifications beyond the treatment of infertility as it is related to the current research on molecular reproductive biology of fertilization and implantation, as well as on stem cell and cloning research. Progress in this area can only be achieved through informed debate among all those involved in ART. This, the most recent WHO meeting in this area, provided one opportunity for such debate. The meeting and this report are not meant to provide solutions to the many problems encountered in the complex subject of assisted reproduction. Rather, they are intended to stimulate further debate among all those interested in the scientific, social and ethical aspects of ART and to provide some guidance and clarification for ongoing discussion.

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Glossary

Aspiration cycle: initiated ART cycle in which one or more follicles are punctured and aspirated irrespective of whether or not oocytes are retrieved.

Assisted hatching: an *in vitro* procedure in which the zona pellucida of an embryo (usually at 8-cell stage or a blastocyst) is perforated by chemical, mechanical or laser-assisted methods to assist separation of the blastocyst from the zona pellucida.

Assisted reproductive technology (ART): all treatments or procedures that include the *in vitro* handling of human oocytes and sperm or embryos for the purpose of establishing a pregnancy. This includes, but is not limited to, *in vitro* fertilization and transcervical embryo transfer, gamete intrafallopian transfer, zygote intrafallopian transfer, tubal embryo transfer, gamete and embryo cryopreservation, oocyte and embryo donation and gestational surrogacy. ART does not include assisted insemination (artificial insemination) using sperm from either a woman's partner or sperm donor.

Birth defect: Structural, functional or developmental abnormalities present at birth or later in life, due to genetic or nongenetic factors acting before birth.

Blastocyst: an embryo with a fluid-filled blastocele cavity (usually developing by five or six days after fertilization).

Cancelled cycle: an ART cycle in which ovarian stimulation or monitoring has been carried out with the intent of undergoing ART but which did not proceed to follicular aspiration, or in the case of a thawed embryo, to transfer.

Clinical abortion: an abortion of a clinical pregnancy which takes place between the diagnosis of pregnancy and 20 completed weeks' gestational age.

Clinical pregnancy: evidence of pregnancy by clinical or ultrasound parameters (ultrasound visualization of a gestational sac). It includes ectopic pregnancy. Multiple gestational sacs in one patient are counted as one clinical pregnancy.

Clinical pregnancy rate: number of clinical pregnancies expressed per 100 initiated cycles, aspiration cycles or embryo transfer cycles. When clinical pregnancy rates are given, the denominator (initiated, aspirated or embryo transfer cycles) must be specified.

Controlled ovarian hyperstimulation (COH): medical treatment to induce the development of multiple ovarian follicles to obtain multiple oocytes at follicular aspiration.

Cryopreservation: freezing and storage of gametes, zygotes or embryos.

Delivery rate: number of deliveries expressed per 100 initiated cycles, aspiration cycles or embryo transfer cycles. When delivery rates are given, the denominator (initiated, aspirated or embryo transfer cycles) must be specified. It includes deliveries that resulted in a live birth and/or stillbirth. The delivery of a singleton, twin or other multiple pregnancy is registered as one delivery.

Early neonatal death: death occurring within the first seven days after delivery.

Ectopic pregnancy: a pregnancy in which implantation takes place outside the uterine cavity.

Embryo: product of conception from the time of fertilization to the end of the embryonic stage eight weeks after fertilization (the term "pre-embryo" or dividing conceptus has been replaced by embryo).

Embryo donation: the transfer of an embryo resulting from gametes that did not originate from the recipient and/or her partner.

Embryo transfer (ET): procedure in which embryo(s) are placed in the uterus or fallopian tube.

Embryo transfer cycle: ART cycle in which one or more embryos are transferred into the uterus or fallopian tube.

Fertilization: the penetration of the ovum by the spermatozoon and fusion of genetic materials resulting in the development of a zygote.

Fetus: the product of conception starting from completion of embryonic development (at eight completed weeks after fertilization) until birth or abortion.

Full-term birth: a birth that takes place at 37 or more completed weeks of gestational age. This includes both live births and stillbirths.

Gamete intrafallopian transfer (GIFT): ART procedure in which both gametes (oocytes and sperm) are transferred to the fallopian tubes.

Gestational age: age of an embryo or fetus calculated by adding 14 days (2 weeks) to the number of completed weeks since fertilization.

Gestational carrier: a woman in whom a pregnancy resulted from fertilization with third-party sperm and oocytes. She carries the pregnancy with the intention or agreement that the offspring will be parented by one or both of the persons that produced the gametes.

Gestational sac: a fluid-filled structure containing an embryo that develops early in pregnancy usually within the uterus.

Hatching: it is the process that precedes implantation by which an embryo at the blastocyst stage separates from the zona pellucida.

Host uterus: see gestational carrier.

Implantation: the attachment and subsequent penetration by the zona-free blastocyst (usually in the endometrium) which starts five to seven days following fertilization.

***In vitro* fertilization (IVF):** an ART procedure which involves *extracorporeal* fertilization.

Infertility: failure to conceive after at least one year of unprotected *coitus.*

Initiated cycles: ART treatment cycles in which the woman receives ovarian stimulation, or monitoring in the case of spontaneous cycles, irrespective of whether or not follicular aspiration is attempted.

Intracytoplasmatic (intracytoplasmic) sperm injection (ICSI): IVF procedure in which a single spermatozoon is injected through the zona pellucida into the oocyte.

Live birth: a birth in which a fetus is delivered with signs of life after complete expulsion or extraction from its mother, beyond 20 completed weeks of gestational age. (Live births are counted as birth events, e.g. a twin or triplet live birth is counted as one birth event.)

Live-birth delivery rate: number of live-birth deliveries expressed per 100 initiated cycles, aspiration cycles or embryo transfer cycles. When delivery rates are given, the denominator (initiated, aspirated or embryo transfer cycles) must be specified. It includes deliveries that resulted in at least one live birth. The delivery of a singleton, twin or other multiple birth is registered as one delivery.

Malformation rate: includes all structural, functional, genetic and chromosomal abnormalities identified in aborted tissue or diagnosed before or subsequent to birth.

Medically assisted conception: conception brought about by noncoital conjunction of the gametes. Includes ART procedures and intrauterine, intracervical and intravaginal insemination with semen of husband/partner or donor.

Micromanipulation (also referred to as **assisted fertilization):** the use of special micromanipulative technol-

ogy that allows operative procedures to be performed on the oocyte, sperm or embryo**.**

Microscopic epididymal sperm aspiration (MESA): procedure in which spermatozoa are obtained from the epididymis, by either aspiration or surgical excision.

Missed abortion: a clinical abortion where the products of conception are not expelled spontaneously from the uterus.

Neonatal death: death within 28 days of birth.

Newborns or infants born: the number of live births plus stillbirths.

Oocyte donation: an ART procedure performed with third-party oocytes.

Preclinical abortion: an abortion that takes place before clinical or ultrasound evidence of pregnancy.

Preclinical pregnancy (biochemical pregnancy): evidence of conception based only on biochemical data in the serum or urine before ultrasound evidence of a gestational sac.

Preimplantation genetic diagnosis (PGD): screening of cells from preimplantation embryos for the detection of genetic and/or chromosomal disorders before embryo transfer.

Preterm birth: a birth which takes place after at least 20, but less than 37, completed weeks of gestation. This includes both live births and stillbirths. Births are counted as birth events (e.g. a twin or triplet live birth is counted as one birth event).

Recipient: in an ART cycle refers to the woman who receives an oocyte or an embryo from another woman.

Spontaneous abortion: spontaneous loss of a clinical pregnancy before 20 completed weeks of gestation or, if gestational age is unknown, a weight of 500 g or less.

Stillbirth: a birth in which the fetus does not exhibit any signs of life when completely removed or expelled from the birth canal at or above 20 completed weeks of gestation. Stillbirths are counted as birth events (e.g. a twin or triplet stillbirth is counted as one birth event).

Surrogate mother: see gestational carrier.

Testicular sperm aspiration (TESA): procedure in which spermatozoa are obtained directly from the testicle, by either aspiration or surgical excision of testicular tissue.

Zygote intrafallopian transfer (ZIFT): procedure in which the zygote, in its pronuclear stage of development, is transferred into the fallopian tube.

Zygote: is the diploid cell, resulting from the fertilization of an oocyte by a spermatozoon, which subsequently develops into an embryo.

This glossary was generated by the International Working Group for Registers on Assisted Reproduction and was further developed and used during this meeting.