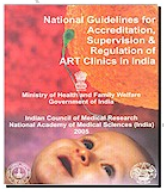
National Guidelines for Accreditation, Supervision & Regulation of ART Clinics in India



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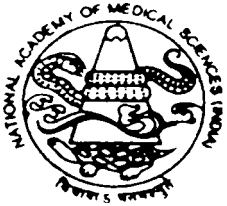
National Guidelines for Accreditation, Supervision and Regulation of ART Clinics in India

Ministry of Health and Family Welfare
Government of India



Indian Council of Medical Research
National Academy of Medical Sciences (India), New Delhi - 110029
2005

National Guidelines for Accreditation, Supervision and Regulation of ART Clinics in India

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Government of India

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Foreword

Shri Prasanna Hota
Secretary
Ministry of Health and Family Welfare
Government of India

Infertility, though not life threatening, can cause intense agony and trauma to the infertile couples. No data on the extent of infertility prevalent in India is available; but the multinational study carried out by WHO (Diagnosis and Treatment of Infertility, ed. P. Rowe and E.N. Vikhlyaeva, 1988) that included India, places the incidence of infertility between 10 and 15%. Out of the population of 1020 million Indians, an estimated 25% (about 250 million individuals) may be conservatively estimated to be attempting parenthood at any given time. By extrapolating the WHO estimates, approximately 13 to 19 million couples are likely to be infertile in the country at any given time. These couples approach ART Clinics.

The increasing demand for ART has resulted in mushrooming of infertility clinics in India. The Assisted Reproductive Technology (ART) in India is being provided by private sector only. Many of these technologies require enormous technical expertise and infrastructure. However, the success rate is below 30% under the best of circumstances. Moreover, it taxes the couple's endurance physically, emotionally and monetarily. Many of these clinics do not have adequate trained manpower and infrastructure facilities to deliver these highly sophisticated technologies and even services provided by some of these clinics are highly questionable. In some cases, the infertile couple are being cheated by providing relatively simple procedure and charged for complicated and expensive procedures. The procedures, wherein Round Spermatid Nuclear Injection and Pre-implantation

Genetic Diagnosis in gender selection of the embryo are used, have not been universally accepted. These issues are of great concern to the society.

In order to regulate and supervise the ART clinics, the Indian Council of Medical Research (ICMR) and National Academy of Medical Sciences (NAMS) have come out with National Guidelines for Accreditation, Supervision and Regulation of ART Clinics in India. These Guidelines have been evolved after detailed discussion and debate by experts, practitioners of ART and public.

I take immense pleasure in presenting these Guidelines, which I strongly feel, would be very useful in regulating and supervising the functioning of ART Clinics and would be helping the ART Clinics in providing safe and ethical services to the needy infertile couples. I also place on record our appreciation of the efforts of the experts of ICMR & NAMS in bringing out these Guidelines.

(Prasanna Hota)
Secretary
Ministry of Health and Family Welfare
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New Delhi-110011

Preface

Prof. N. K. Ganguly
Director General
Indian Council of Medical Research

The successful birth of the world's first baby conceived by *in vitro* fertilization (IVF) and embryo transfer occurred on July 25, 1978, in the UK. The world's second IVF baby was born 67 days later on October 3, 1978 in Kolkata. India's first scientifically documented IVF baby was, however, born on August 6, 1986 in Mumbai through the support of the Indian Council of Medical Research. Since then, over one and half million babies conceived by Assisted Reproductive Technologies (ART) have reportedly been born throughout the world.

The advent of any new technology that affects mankind raises several technical and moral dilemmas and poses many ethical and technical challenges. ART is no exception. In the Indian context where barrenness is looked down upon, infertile patients look up to ART as the last resort to parenthood. Some of them are prepared to go to any extent to achieve their life's ambition. Unfortunately, ART has not reached a stage where all forms of infertility can be treated, nor can any clinic offer a 100% success if the couples were to undergo any of the assisted reproductive technologies. The ART practitioner is often faced with a technical challenge of trying to select the right treatment for a particular type of infertility, knowing fully well that none of the available techniques offer 100% success. The practitioner also faces moral responsibility of trying to convince the infertile couple of this fact and let them know the chances of success and failure by the particular treatment that is being offered.

The increasing demand for ART has resulted in mushrooming of infertility clinics in India. There is no reliable information on the number of ART clinics in India in the absence of a national registry of ART clinics. There is no information on the follow-up of babies born after the use of ART to know the incidence of congenital malformation in them. There have been reports in the press of malpractices carried out by some ART clinics.

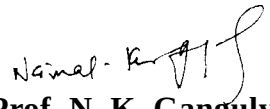
Such malpractices are not unique to India but are a global phenomenon. Many countries have taken steps to prevent such aberrant occurrences. Austria, Australia, Brazil, Canada, the Czech Republic, Denmark, France, Germany, Greece, Hungary, Iceland, Israel, Italy, Japan, Korea, Mexico, the Netherlands, Norway, Saudi Arabia, Singapore, South Africa, Spain, Sweden, Switzerland, Taiwan and Turkey have legislations for the practice of ART. Scientific societies in Finland, Poland, Portugal and the USA have drawn up guidelines for the practices of ART. Argentina, Egypt and the UK have both guidelines and legislation. Guidelines and/or legislation in these countries have been shown to improve the process of patient care and procedure outcomes.

There are no guidelines for the practice of ART, accreditation of infertility clinics and supervision of their performance in India. This document aims to fill this lacuna and also provide a means of maintaining a national registry of ART clinics in India. The document has been widely publicized, discussed and debated by expert groups of the ICMR and the National Academy of Medical Sciences and then by practitioners of ART and the public in Chennai, Jodhpur, Kolkata, Bangalore, Hyderabad and Mumbai. These discussions involved over 4000 participants including doctors, scientists, bureaucrats, legal experts, infertile couples and the general public. This document was also put on the Council's website and elicited many comments and responses.

All attempts have been diligently made to encompass all points of view and bring out a document that conveys the views of the vast majority of participants in the above mentioned discussions and debates.

This document should be useful to the infertility clinics as well as to those who seek the services of such clinics. However, as ART is an evolving field, this

document will need to be periodically reviewed. This will be a challenging task both for the practitioners of ART and the regulatory authority that is yet to be established.



(Prof. N. K. Ganguly)
Director General
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New Delhi-110029

Acknowledgements

The Council gratefully acknowledges the valuable contribution of all the members of the Expert Committee responsible for formulating these guidelines, for providing continued guidance in drafting and finalizing the guidelines. We are extremely grateful to the Chairpersons of the subcommittees of the Expert Committee for conducting regional discussions and preparing the draft document on the respective topics assigned to them.

This document is a concerted effort made possible by the advice, assistance and co-operation of many individuals, institutions and government and non-governmental organizations, specially the National Academy of Medical Sciences (NAMS), The Medically Aware and Responsible Citizens of Hyderabad (The MARCH), Indian Society for the Study of Reproduction and Fertility (ISSRF) and Federation of Obstetrics and Gynaecology Society of India (FOGSI).

The suggestions and advice emerging from the workshop sponsored by the National Academy of Medical Sciences held on 16th September 2001 at Bangalore were of great significance. Therefore, the Council is particularly grateful to the participants of the NAMS workshop (i.e. Manohar, Aruna Sivakami, J Mehta, S. Narang, M. S. Sreenivas, M. Gourie Devi, B. Kalyan, N. Krishnan, N. Pandiyan, K. S. Jayaraman, P. B. Seshagiri, R. H. Mehta, Seema Singh, P. V. Kulkarni, Lalitha, P. Sarkar, M. Sarkar, M. Priya, K. Nath, M. Nirad, D. Raghunath, Gopinathan, R. S. Sharma, N. C. Saxena, V. Muthuswamy, B. N. Chakravarthy, C. S. Bhaskaran, M. Rajalakshmi and T. C. Anand Kumar).

Special thanks are due to Dr. P. M. Bhargava not only for his initiative, professional and editorial inputs and consistent interest in and enthusiasm for the guidelines, but also doing everything in good humour, inspite of continual office interruptions and information overload on the various topics of the guidelines.

We are also grateful to the National Commission for Women and the National Human Rights Commission for their valuable advise.

Secretarial assistance provided by Mr. Mahesh Kumar is gratefully acknowledged.

Abbreviations

AIDS	-	Acquired Immune Deficiency Syndrome
ASRM	-	American Society for Reproductive Medicine
AI	-	Artificial Insemination
AID	-	Artificial Insemination with Donor Semen
AIH	-	Artificial Insemination with Husband's Semen
ART	-	Assisted Reproductive Technology
BBT	-	Basal Body Temperature
CO_2	-	Carbon Dioxide
CC	-	Clomiphene Citrate
CASA	-	Computer-Aided Sperm Analysis
CBAVD	-	Congenital Bilateral Absence of Vas Deferens
CMV	-	Cytomegalo Virus
DHEA	-	Dehydro-epiandrostendione
DNA	-	Deoxyribonucleic Acid
DMSO	-	Dimethylsulfoxide
ED	-	Embryo Donation
ELSNI	-	Elongated Spermatid Nuclear injection
ESHRE	-	European Society for Human Reproduction and Embryology
FISH	-	Fluorescent *in situ* Hybridization

FSH - Follicle Stimulating Hormone

GIFT - Gamete Intrafallopian Transfer

GnRH - Gonadotropin Releasing Hormone

GLP - Good Laboratory Practices

HBV - Hepatitis B Virus

HCV - Hepatitis C Virus

hCG - Human Chorionic Gonadotropin

hMG - Human Menopausal Gonadotropin

HIV - Human Immunodeficiency Virus

HOST - Hypo-Osmotic Swelling Test

ICMR - Indian Council of Medical Research

ICPD - International Conference for Population and Development

IFFS - International Federation of Fertility Societies

ICSI - Intracytoplasmic Sperm Injection

IUI - Intra-uterine Insemination

IRR - Institute for Research in Reproduction, (now National Institute for Research in Reproductive Health, NIRRH)

IVF-ET - *In vitro* Fertilization–Embryo Transfer

IVMTS - *In vitro* Maturation of Testicular Sperm

LH - Luteinizing Hormone

OD	-	Oocyte Donation
OT	-	Operation Theatre
OHS	-	Ovarian Hyperstimulation Syndrome
PESA	-	Percutaneous Epididymal Sperm Aspiration
PGD	-	Pre–implantation Genetic Diagnosis
PCOS	-	Polycystic Ovarian Syndrome
PCR	-	Polymerase Chain Reaction
RNA	-	Ribonucleic Acid
SCMPT	-	Sperm Cervical Mucous Penetration Test
SOP	-	Standard Operating Procedure
TESA	-	Testicular Sperm Aspiration
TESE	-	Testicular Sperm Extraction
TSH	-	Thyroid Stimulating Hormone
TVS	-	Transvaginal Sonography
UPS	-	Uninterrupted Power Supply
WHO	-	World Health Organization
WMA	-	World Medical Assembly

Corrigendum

(1) 1.2.1 Artificial Insemination (AI)

AI is the procedure of artificially transferring semen into reproductive system of a woman. This technique comprises artificial insemination with husband's (AIH) or with donor sperm (AID). (Page No. 5)

(2) 1.5.5 Programme co-ordinator/director

This should be a senior person who has had considerable experience in handling all aspects of ART. (Page No. 23)

(3) 1.6 ART Procedure

"National Accreditation Committee" appearing in para 1.6 may be read as "National Advisory Committee". (Page No. 24)

(4) 1.6.10 The future ART technologies

"National Accreditation Committee" appearing in para 1.6.10 may be read as "National Advisory Committee". (Page No. 32)

(5) 3.14.7 The State Government would close down any unregulated clinics not satisfying the above criteria. (Page No. 73)

(6) 3.15 Responsibilities of the Accreditation Authority

The para 3.15 may be read as follows:

3.15 Responsibilities of the Accreditation/Appropriate Authority

3.15.1 State Accreditation Authority :

A State Accreditation Authority will be set up by the State /UT Governments through their Department of Health and /or Family Welfare to oversee all matters relating to accreditation, supervision and regulation of ART Clinics in the States/UTs in accordance with the Guidelines. The functions of the Accreditation Authority, inter-alia, include-

i) to review the activities of Appropriate Authorities functioning in the State and take appropriate action against them;
ii) to monitor the implementation of the provision of the Guidelines by ART clinics;
iii) to order closure of an ART Clinic if the ethical Guidelines and operative procedures laid down in the Guidelines are not followed.

3.15.2 Appropriate Authority.

The State Government may also set up one or more Appropriate Authorities for implementation of the Guidelines for the whole or a part of the State having regard to the number of ART Clinics. Functions of the Appropriate Authority are:

- to grant or suspend registration of an ART Clinic;
- to enforce the provisions of the Guidelines by ART Clinics;
- to investigate complaints of breach of the Guidelines;
- to visit any ART Clinic/Centre accredited or not accredited, once a year with or without prior information

to the clinic/centre, to determine if the ethical guidelines and operative procedures are being followed. If not, the Authority will point out lapses to the clinic/centre in writing. If these lapses continued for a maximum period of six months (during which period that clinic shall not engage in any activity related to the lapses), the Appropriate Authority would recommend to the State Accreditation Authority that the clinic/centre may be ordered to be closed;

- to impose a fine or a penalty on the clinic/centre for violation of any provisions of Guidelines as per delegation of powers by the State Accreditation Authority;
- to visit and regulate semen banks in the manner mentioned above;
- any other function as directed by Accreditation Authority

3.15.3 Complaints Redressal Mechanism

A client of an ART Clinic or any other person can file a complaint against an ART Clinic for breach of any provisions of the Guidelines or in respect of any related matter to the Appropriate Authority. The Appropriate Authority shall investigate such complaints and take appropriate action under intimation to the complainant.

3.15.4 Central Advisory Committee

Ministry of Health and Family Welfare, Government of India will set up a National Advisory Committee under the Chairmanship of Secretary, Health & Family Welfare and Director General, ICMR as Co-chairman. The composition of the Committee is given in Chapter 9. The National Advisory Committee will review and monitor the implementation of the

Guidelines and advise the Central Government on all policy matters relating to regulation of ART Clinics.

(7) 3.16.4 Rights of an unmarried woman to AID

Para 3.16.4 is to be deleted. (Page No. 75)

(8) 5.0 Training

The last three lines of page 101 may be read as: Such conference must be encouraged through organization such as the Indian Council of Medical Research (ICMR), Department of Science and Technology (DST), Department of Biotechnology (DBT), Council of Scientific and Industrial Research (CSIR) and the various science academies in India. (Page 101)

(9) 9.0 Composition of the National Advisory Committee.

Executive Secretary: A Officer not below the rank of Joint Secretary in the Ministry of Health and Family Welfare, Govt. of India. (Page 117)

Chapter 1

Introduction, Brief History of ART and Requirements of ART Clinics

1 Introduction

Infertility, though not life threatening, causes intense mental agony and trauma that can only be best described by infertile couples themselves. There are no detailed figures of the extent of infertility prevalent in India but a multinational study carried out by WHO (Diagnosis and treatment of infertility, ed. P. Rowe and E. M. Vikhlyaeva, 1988) that included India, places the incidence of infertility between 10 and 15%. Out of a population of 1000 million Indians, an estimated 25% (250 million individuals) may be conservatively estimated to be attempting parenthood at any given time; by extrapolating the WHO estimate, approximately 13 to 19 million couples are likely to be infertile in the country at any given time.

Prevention and appropriate treatment of infertility has been included in the ICPD (International Conference on Population and Development) Programme of Action; it follows that alleviation of infertility should be included as a component of the primary health care system. Most types of infertility such as reproductive tract infections (RTI) and genital tuberculosis, are preventable and amenable to treatment. About 8% of infertile couples, however, need serious medical intervention involving the use of advanced ART (Assisted Reproductive Technologies) procedures such as IVF (*In virto* Fertilization) or ICSI (Intracytoplasmic Sperm Injection). Such advanced treatment is expensive and not easily affordable to the majority of Indians. Further, the successful practice of ART requires considerable technical expertise and expensive infrastructure. Moreover, the success rate of any ART procedure is below 30% under the best of circumstances. Infertility, specially in our country, also has far-reaching societal implications. Therefore, with the rapidly increasing use of ART in our country, it has become imperative to ensure their safety and have safeguards against their possible misuse.

Scientific societies around the world, such as the ASRM, ESHRE and IFFS, have drawn up guidelines for the safe and ethical practice of ART. The European Union and the Governments of several countries such as Australia, the UK and the USA have taken steps to accredit and supervise the performance of infertility clinics.

At present here are neither guidelines nor a legislation in regard to the practice of ART in India. This document aims to fill this lacuna. It has been prepared after extensive consultations held at both the ICMR and other national institutions, with scientists, medical practitioners, lawyers, social scientists and activists.

The present guidelines are meant to ensure that ART clinics in India are accredited, regulated and supervised to assure the patients as well as the public that our ART clinics offer services that are at par with those available anywhere in the world. Medical malpractice now comes under the purview of the legal redressal machinery of the country; this makes it all the more necessary to have national guidelines for the practice of ART.

1.1 Brief History of IVF in India

The world's first IVF baby, Louise Brown, was born on July 25, 1978, in the UK through the efforts of Dr. Robert G Edwards and Dr. Patrick Steptoe. The world's second and India's first IVF baby, Kanupriya, alias Durga, was born 67 days later on October 3, 1978, through the efforts of Dr. Subhas Mukherjee and his two colleagues in Kolkata.

Dr. Mukherjee and his colleagues published a short note on their above work, in the Indian Journal of Cryogenics (Vol. 3: page 80, 1978). The techniques used by Mukherjee were markedly different from those used by Edwards and Steptoe. Mukherjee was the first person in the world to use

(a) gonadotropins for ovarian stimulation prior to ovum pick-up in an IVF treatment cycle;

(b) the transvaginal route by colpotomy for harvesting oocytes; and

(c) freezing and thawing of human embryos before transferring them into the uterus that led to the successful birth of Durga.

India's first scientifically documented IVF baby, Harsha, was born on August 6, 1986, in Mumbai, through the collaborative efforts of the ICMR's Institute for Research in Reproduction and the King Edward's Memorial Hospital (KEM). This work was executed after being approved by the

Scientific Advisory Committee of the ICMR's Institute for Research in Reproduction and the Ethics Committee for Human Experimentation of the KEM Hospital. Full details of this and other studies in this area were published in the ICMR Bulletin (1986: No. 16) and in peer reviewed national (Natl. Med. J. India 1:10, 1988) and international journals (J. *In vitro* Fertilization & ET 5:376, 1988). Births of IVF babies were reported subsequently during the same year by two other clinics in India. There are an estimated 250 IVF clinics in India today.

1.1.1 ART - an alternative to reversal of Sterilization

Infertility, consequent to use of terminal methods of contraception under the Family Planning Programme, may sometimes need to be reversed for personal reasons such as having lost a child/children born prior to sterilization. IVF is one of the options for women in whom fallopian tubes have been surgically severed and where recanalisation for correction of infertility has failed.

1.2 Definitions

1.2.1 Artificial Insemination (AI)

AI is the procedure of transferring semen into the reproductive system of a woman. This technique comprises artificial insemination with husband's (AIH) or with donor sperm (AID).

1.2.2 Aspiration cycle

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

1.2.3 Assisted Hatching

Assisted hatching allows easier release of the embryo from its shell (zona pellucida), helping implantation and increasing the pregnancy rate.

1.2.4 Assisted Reproductive Technology (ART)

For the purpose of these guidelines, ART would be taken to encompass all techniques that attempt to obtain a pregnancy by manipulating the sperm or/ and oocyte outside the body, and transferring the gamete or embryo into the uterus.

1.2.5 Blastocyst

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

1.2.6 Controlled ovarian hyperstimulation (COH)

Medical treatment to induce the development of multiple ovarian follicles to obtain multiple oocytes at follicular aspiration.

1.2.7 Cryopreservation

Freezing and storage of gametes, zygotes or embryos

1.2.8 Donation of Gametes

Donation of gametes is a process by which a person voluntarily offers his or her gametes for the process of procreation.

1.2.9 Ectopic pregnancy

A pregnancy in which implantation takes place outside the uterine cavity

1.2.10 Embryo

Embryo is defined as the fertilized ovum that has begun cellular division and continued development up to the blastocyst stage till the end of eight weeks.

1.2.11 Embryo donation

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

1.2.12 Embryo transfer (ET)

Procedure in which embryo(s) are placed in the uterus or fallopian tube.

1.2.13 Fertilization

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

1.2.14 Foetus

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

1.2.15 Foetal Reduction

Foetal reduction is an invasive/interventional process by which a higher order multiple pregnancy is reduced to a single or twin pregnancy in order to improve the perinatal outcome.

1.2.16 Gamete

Oocytes and sperm are called gametes.

1.2.17 Hatching

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

1.2.18 ICSI (Intracytoplasmic Sperm Injection)

In ICSI, a single sperm is injected into the cytoplasm of the ovum to effect fertilization, before the fertilized ovum is transferred to the uterus of the woman.

1.2.19 Implantation

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

1.2.20 Infertility

Failure to conceive after at least one year of unprotected *coitus*

1.2.21 Intrauterine Insemination (IUI)

Intrauterine Insemination involves the introduction of sperm into the uterus of the woman. In IUI, specially prepared sperm are injected into the uterine cavity via a fine cannula passed through the cervix. At this site, the sperm are near the uterine entrance of each of the two fallopian tubes and thus have a shorter distance to swim in order to reach the oocyte(s) released at the time of ovulation.

1.2.22 IVF-ET (*In vitro* Fertilization-Embryo Transfer)

In vitro Fertilization-Embryo Transfer (IVF-ET) is the fertilization of an ovum outside the body and the transfer of the fertilized ovum to the uterus of a woman.

1.2.23 IVMTS & IVMO (*In vitro* Maturation of Testicular Sperm and *In vitro* Maturation of Oocytes)

In vitro Maturation of Testicular Sperm (IVMTS) involves keeping the testicular sperm in a culture medium under optimal conditions where they can attain physiological maturity and acquire motility.

In vitro maturation of immature oocytes involves keeping the immature oocytes in an appropriate culture medium under optimal conditions where they can attain physiological maturity.

1.2.24 Oocyte donation

An ART procedure performed with third-party oocytes

1.2.25 Ovum/Oocyte

Ovum/oocyte is the female gamete produced in the ovary.

1.2.26 PESA (Percutaneous Epididymal Sperm Aspiration) and TESA/TESE (Testicular Sperm Aspiration/ Extraction)

Percutaneous Epididymal Sperm Aspiration (PESA) and Testicular Sperm Aspiration (TESA) are simplified, minimally invasive outpatient procedures that allow the physician to recover the sperm for fertilization in patients with obstructive azoospermia (lack of sperm in semen).

PESA requires a needle to be introduced into the epididymis and the contents aspirated. The aspirate is observed under the microscope to determine if motile sperm are present.

In TESA, the needle is introduced into the testicle itself.

1.2.27 Pre–implantation Genetic Diagnosis (PGD)

Pre–implantation Genetic Diagnosis is a technique in which an embryo formed through IVF is tested for specific genetic disorders (e.g. cystic fibrosis) or other characteristics prior to implantation.

1.2.28 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).

1.2.29 Semen

A thick, whitish fluid discharged through the penis during ejaculation containing spermatozoa, secretions from the testes, seminal vesicles, prostate gland, bulbo-uretheral and other glands associated with the male reproductive system.

1.2.30 Semen Donor

Semen obtained from third party for purpose of inseminating the wife in cases where husband is unable to produce healthy semen.

1.2.31 Sperm

Sperm are the male gametes produced in the testicles.

1.2.32 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.

1.2.33 Surrogacy

Surrogacy is an arrangement in which a woman agrees to carry a pregnancy that is genetically unrelated to her and her husband, with the intention to carry it to term and hand over the child to the genetic parents for whom she is acting as a surrogate.

1.2.34 Surrogacy with Oocyte Donation

Surrogacy with oocyte donation is a process in which a woman allows insemination by the sperm/semen of the male partner of a couple with a view to carry the pregnancy to term and hand over the child to the couple.

1.2.35 Zygote

Fertilized oocyte prior to first cell division is called zygote

1.3 Minimal Physical Requirements for an ART Clinic

A well designed ART clinic of Level 2 or Level 3 (Sections 2.5.3 and 2.5.4) should have a non-sterile and a strictly sterile area as detailed below. Some of the spaces mentioned below could be combined (that is, the same space may be used for more than one purpose) as long as such a step does not compromise the quality of service. However, the space provision for the sterile area cannot be combined with those for the non-sterile area and vice-versa. For level 1B infertility care units (section 2.5.2), a strictly sterile area will not be required. The space requirement, however, will include, a reception area, a waiting room for the patients, a consulting room for the gynaecologist, and requirements mentioned under 1.3.1.8, 1.3.1.9 and 1.3.1.10.

1.3.1 The non-sterile area

The non-sterile area must include what is listed under 1.3.1.1 to 1.3.1.9 below.

1.3.1.1 A reception and waiting room for patients

1.3.1.2 A room with privacy*:* A room with privacy for interviewing and examining male and female partners independently is essential. Evaluation of infertility necessitates history taking of the most intimate sexual practices between the couples. This is followed by close examination of the reproductive tract and sexual organs. Adequate measures must be taken to ensure that history taking and examination are carried out in strict privacy, maintaining the dignity of the patients. In case a male doctor examines a female patient, there must always be a female attendant present. The room must be

equipped with an examination table and gynecological instruments for examining the female per vaginum, an appropriate ultrasonographic machine with a probe for transvaginal examination of the female and examination of the testes and excurrent male reproductive tract. A colour Doppler would be useful but not essential.

1.3.1.3 A general-purpose clinical laboratory

1.3.1.4 Store room: A well-stocked store for keeping essential stock of especially those items that have to be imported, precluding the need to be caught short in the middle of treatment. Facilities must be available for storing sterile (media, needles, catheters, petri dishes and such-like items) and non-sterile material under refrigerated and non-refrigerated conditions as appropriate.

1.3.1.5 Record room: Record keeping must be computerized as far as possible so that data is accessible retrospectively for analysis or when called upon by the supervisory agency. There are many software programmes for this purpose, which are commercially available today. A user-friendly one should be chosen that could be used widely. Besides containing essential details of the patient's records, it must contain history of the cause of infertility as diagnosed earlier, results of new diagnosis if relevant, the treatment option best suited for the particular patient, the treatment carried out and the outcome of treatment, and follow-up if any. Any other noteworthy point such as possible adverse reaction to drugs, must be recorded. ICMR should make an effort to devise a form for basic data recording, which would be suitable for India.

1.3.1.6 Autoclave room: A separate facility must be available for sterilizing and autoclaving all surgical items as well as some of those to be used in the *in vitro* culture laboratory.

1.3.1.7 Steps for vermin proofing: Adequate steps should be taken to make the whole clinic vermin proof, with suitable traps for preventing insects and other forms of unwanted creatures entering the clinic.

This essential detail should be planned at an early stage because no pesticide can be used in a fully functional IVF clinic, as it could be toxic to the gametes and embryos.

1.3.1.8 Semen collection room: This must be a well-appointed room with privacy and an appropriate environment; it should be located in a secluded area close to the laboratory. Such a facility must be available in-house rather than having the patient collect the sample and bring it to the laboratory for analysis as, in the latter case, semen quality and identity is likely to be compromised. Procedures for collection of semen as described in the WHO Semen Analysis Manual must be followed with special reference to the type of container used; these containers must be sterile, maintained at body temperature and non-toxic. This room must have a washbasin with availability of soap and clean towels. The room must also have a toilet and must not be used for any other purpose.

1.3.1.9 Semen processing laboratory: There must be a separate room with a laminar air flow for semen processing, preferably close to the semen collection room. This laboratory must also have facilities for microscopic examination of post-coital test smears. Good Laboratory Practice (GLP) guidelines as defined internationally must be followed. Care must be taken for the safe disposal of biological waste and other materials (syringes, glass slides, etc.). Laboratory workers should be immunized against hepatitis B and tetanus.

1.3.1.10 Clean room for IUI: There must be a separate area/room with an appropriate table for Intra-Uterine Insemination (IUI).

1.3.2 The sterile area

The sterile area shall house the operation theatre, a room for intrauterine transfer of sperm or embryos and an adjoining embryology laboratory. Entry to the sterile area must be strictly controlled by an anteroom for changing footwear, area for changing into sterile garments and a scrub-station. The sterile area must be

air-conditioned where fresh air filtered through an approved and appropriate filter system is circulated at an ambient temperature (22-25^{0} C).

1.3.2.1 The operation theatre: This must be well equipped with facilities for carrying out surgical endoscopy and transvaginal ovum pick-up. The operation theatre must be equipped for emergency resuscitative procedures.

1.3.2.2 Room for intrauterine transfer of embryo: This room must be a sterile area having an examination table on which the patient can be placed for carrying out the procedure and rest undisturbed for a period of time.

1.3.2.3 The embryology laboratory complex: The embryology laboratory must have facilities for the control of temperature and humidity and must have filtered air with an appropriate number of air exchanges per hour. Walls and floors must be composed of materials that can be easily washed and disinfected; use of carpeting must be strictly avoided. The embryology laboratory must have the following:

- a laminar flow bench with a thermostatically controlled heating plate
- a stereo microscope
- a routine high-powered binocular light microscope
- a 'high resolution' inverted microscope with phase contrast or Hoffman optics, preferably with facilities for video recording
- a micromanipulator (if ICSI is done)
- a CO_2 incubator, preferably with a back up
- a hot air oven
- a laboratory centrifuge
- equipment for freezing embryos in a programmed manner
- liquid nitrogen cans

- a refrigerator

Appropriate steps need to be taken for the correct identification of gametes and embryos to avoid mix-ups. All material from the operation room, culture dishes and Falcon tubes for sperm collection (including lids), must bear the name of the patient. In the incubator, identified oocytes and sperm should be kept together on the same tray and double-checked. Pipettes used should be disposed off immediately after use. The embryology laboratory must have a daily logbook in which all the day's activities are recorded, including the performance of the equipment.

1.3.3 Ancillary laboratory facilities

The infertility clinic need not have in-house facilities to perform all the procedures necessary to diagnose infertility, such as those mentioned below. They can be farmed out to speciality laboratories specializing in delivering such services, as long as they are located in the neighborhood.

1.3.3.1 Hormone and other assays: The infertility clinic must have ready access to laboratories that are able to carry out immunoassays of hormones (FSH, LH, Prolactin, hCG, TSH, Insulin, Estradiol, Progesterone, Testosterone and DHEA) and tests such as for HIV and Hepatitis B. Endocrine evaluation constitutes an essential diagnostic procedure to determine the cause of infertility. It is also necessary to estimate blood estradiol in samples taken from a woman undergoing controlled ovarian hyperstimulation, and have the result on the same day to determine the dose of drugs to be given for induction of ovulation. Accurate monitoring of endocrine response to controlled ovarian stimulation goes a long way in preventing ovarian hyperstimulation.

1.3.3.2 Microbiology and histopathology: Another important facility in an ART clinic (or easily accessible to it) would be that of a microbiology laboratory that can carry out rapid tests for any infection,

and a clinical chemistry laboratory. Facilities for carrying out histopathological studies on specimens obtained from the operation theatre would also be desirable.

1.3.3.3 Maintenance of the laboratories: Each laboratory should maintain in writing, standard-operating manuals for the different procedures carried out in the laboratory. It should be ensured that there is no "mix up" of gametes or embryos. The patient's name should be clearly labeled on all the tubes, dishes and pipettes containing the gametes and embryos. All pipettes should be immediately discarded after use.

Laminar flowhoods, laboratory tables, incubators and other areas where sterility is required must be periodically checked for microbial contamination using standard techniques, and a record of such checks must be kept.

A logbook should be maintained which records the temperature, carbon dioxide content and humidity of the incubators and the manometer readings of the laminar air flow.

All instruments must be calibrated periodically (at least once every year) and a record of such calibration maintained.

1.3.3.4 Quality of consumables used in the laboratory: All disposable plasticware must be procured from reliable sources after ensuring that they are not toxic to the embryo. Culture media used for processing gametes or growing embryos *in vitro* should be preferably procured from reliable manufacturers. Each batch of culture medium needs to be tested for sterility, endotoxins, osmolality and pH. The embryologist should know the composition of the media that are being used. Most media are supplemented with serum; they should, therefore, be tested for antibodies to HIV 1 and 2, Hepatitis B Surface Antigen and Hepatitis C RNA.

1.4 Back-up Power Supply

There should be no interruption in power supply to the incubator and to other essential services in the clinic. Given the power supply situation in India, it is, therefore, imperative that a power back up in the form of UPS systems and/or a captive power generation system is available in infertility clinics offering ART services.

1.5 Essential Qualifications of the ART Team

The practice of ART requires a well-orchestrated teamwork between the **gynaecologist, the andrologist and the clinical embryologist** supported by a **counsellor** and a **programme coordinator/director**. The staff requirements given below would be mandatory for Level 2 and Level 3 clinics (see Section 2.5.3 and 2.5.4). In the case of small Level 2 and Level 3 clinics, the services of the andrologist, the clinical embryologist and/or the counsellor could be shared.

1.5.1 Gynaecologist

The minimal qualification for a gynaecologist in a Level 1B, Level 2 or Level 3 clinic (see Sections 2.5.2, 2.5.3 and 2.5.4) is a post-graduate diploma or degree in gynaecology. Additional experience should include:

- © Understanding the causative factors of male and female infertility.
- © Acquiring knowledge of the practice and use of diagnostic methods for determining the cause of infertility.
- © Acquiring knowledge of the clinical aspects of reproductive endocrinology and the reproductive defects caused by endocrine factors, and an understanding of the limitations of the currently used hormone assay methods, and of the techniques available for medically or surgically correcting endocrine disorders.
- © Acquiring competence/skills in gynecological ultrasonography to diagnose reproductive tract anomalies, monitoring ovarian and uterine response to ovarian stimulation, picking up oocytes at the most appropriate time, and transferring embryos by any one of the several methods currently available to handle embryo transfer in

'difficult cases'.

© The gynaecologist must be well versed, particularly in the pharmacology of hormone action, and know how to avoid situations such as Ovarian Hyperstimulation Syndrome that can pose a great health hazard.

The responsibilities of the gynaecologist would include the following:

- Interviewing of the infertile couple initially.
- History taking.
- Physical examination of the female.
- Recommending appropriate tests to be carried out, interpreting them and treating medical disorders (infections, endocrine anomalies).
- Carrying out laparoscopy or sonohysterosalpingography for determining the status of the uterus and the fallopian tube.
- Advising the couple on planned relationship in simple cases.
- Carrying out AIH, AID, IUI, IVF or ICSI as the case may warrant, based on diagnostic evidence.

In case of male factor infertility, if the gynaecologist is confident and competent, he/she can treat such cases or refer them to the andrologist. The treating doctor must be responsible for maintaining all records of diagnosis, treatment given and consent forms. Before any treatment is given, it is advisable that the couple is referred to the counsellor, with all the details of the case, for proper advise and counselling. It would be the gynaecologist's responsibility to see that all equipment and instruments in the operation theatre are properly functional and in order, and that a logbook is maintained of their use and operation.

1.5.2 Andrologist

Fifty percent of infertility cases are related to male factors, many of which can be treated by specific ART procedures or other less invasive procedures. Andrology, a subject related to male reproduction, does not constitute a formal course in the medical curriculum in India, although several journals in andrology are published from different parts of the world including China. There is also an International Andrological Society with branches or affiliated societies all over the world. In India it is the urologist with a post-graduate degree in urology that often takes on the task of treating male infertility. Such individuals must receive additional training in diagnosis of various types of male infertility covering psychogenic impotence, anatomical anomalies of the penis which disable normal intercourse, endocrine factors that cause poor semen characteristics and/or impotence, infections, and causes of erectile dysfunction.

- The andrologist must have knowledge of the occupational hazards, infections and fever that cause reversible or irreversible forms of infertility, and knowledge of ultrasonographic or vasographic studies of the reproductive excurrent ducts to detect partial occlusion that can be surgically corrected.
- He/she must understand the principles of semen analysis and their value and limitation in diagnosis of male fertility status. The person should also be able to interpret the fertility status of the male from the result of semen analysis. The andrologist must be able to collect semen by prostatic massage for microbial culture in cases where infection may lie in the upper regions (prostate, seminal vesicles) of the reproductive tract. He/she should also be able to collect spermatozoa from the excurrent ducts or testis for use in ICSI and must also be knowledgeable about the genetic implications of using poor-quality sperm for ICSI as this technique can vertically transfer the genetic defects of the father to the child. He/she should be familiar with the surgical procedures available for correcting an anatomical defect in the reproductive system such as epididymo-vasal re-anastmosis and varicocoelectomy.

© An individual may act as an andrologist for more than one clinic but each clinic where the andrologist works must own responsibility for the andrologist and ensure that the andrologist is able to take care of the entire work load of the clinic without compromising on the quality of service.

The responsibilities of the andrologist would include the following:

- Recording case histories.
- Prescribing appropriate diagnosis and treatment based on the diagnosis.
- Carrying out such surgical procedures as warranted by the diagnosis.
- Maintaining all the records, from the case history to the treatment given, and the patient consent forms.
- Referring the couple to the gynaecologist for carrying out the appropriate ART procedure if necessary, after the male factor has been duly investigated.
- Referring the couple to the counsellor if necessary.
- In cases of surgical intervention, making sure that the operation theatre is fully functional and all supplies are available before the start of any surgical procedure.
- Entering any deficiency that needs attention in the operation theatre logbook.

1.5.3 Clinical Embryologist

The **clinical embryologist** must be knowledgeable in mammalian embryology, reproductive endocrinology, genetics, molecular biology, biochemistry, microbiology and *in vitro* culture techniques. The biologist must also be familiar with ART. He/she must be either a medical graduate or have a post-graduate degree or a doctorate in an appropriate area of life sciences. (In the case of a clinic in existence for at least one year before the promulgation

of these guidelines, a person with a B Sc or BV Sc degree but with at least five years of first-hand, hands-on experience of the techniques mentioned below and of discharging the responsibilities listed below, would be acceptable for functioning as a clinical embryologist in the particular clinic. Such persons would also be eligible to take a test to be designed and conducted by an appropriate designated authority, to qualify for a position of a clinical embryologist in a new clinic.) He/she must be familiar with the following:

- © Principles and practice of semen analysis and cryopreservation of semen.
- © Cytology of mammalian and human oocyte to identify stages of oocyte maturation accurately.
- © All aspects of embryology including developmental biology.
- © Cell biological techniques used in cell and tissue culture.
- © Molecular biology and genetics of human reproduction.
- © Micromanipulation of sperm and oocytes for carrying out ICSI and single-cell biopsies of embryos for preimplantation genetic diagnosis.
- © Principles and functioning of all the equipment used in the laboratory.
- © In vitro fertilization of oocytes after processing the gametes.
- © Principles and practice of embryo freezing.

The responsibilities of the clinical embryologist would be:

- To ensure that all the necessary equipments are present in the laboratory and are functional.
- To perform all the procedures pertaining to processing, handling and culturing of gametes and embryos in the laboratory and hand over the embryo to the gynaecologist.
- To maintain records of all the procedures carried out in the laboratory.
- In case of shortage of adequately trained clinical embryologists, an

individual may act as a clinical embryologist for more than one clinic but each clinic where the person works must own responsibility for the embryologist and ensure that the embryologist is able to take care of the entire work load of the clinic without compromising on the quality of service. An embryologist must not be associated with more than two centers at any given time.

1.5.4 Counsellors

Counsellors are an important adjunct to any infertility clinic. Indeed, in the UK, counsellors are appointed by the clinic but they report to an independent body. This ensures that there is fair play by the clinic and the patients are adequately informed of what and what not to expect from the treatment offered to them. Counselling for ART is not taught as a separate subject anywhere. A person who has at least a degree (prefarably a postgraduate degree) in Social Sciences, Psychology, Life Sciences or Medicine, and a good knowledge of the various causes of infertility and its social and gender implications, and the possibilities offered by the various treatment modalities, should be considered as qualified to occupy this position. The person should have a working knowledge of the psychological stress that would be experienced by potential patients, and should be able to counsel them to assuage their fears and anxiety and not to have unreasonable expectations from ART. A member of the staff of an ART clinic who is not engaged in any other full-time activity in the clinic can act as a counsellor.

The counsellor must invariably appraise the couple of the advantages of adoption as against resorting to ART involving a donor. An individual may act as a counsellor for more than one clinic but each clinic where the counsellor works must own responsibility for the counsellor and ensure that the counsellor is able to take care of the entire counselling load of the clinic without compromising on the quality of the counselling service.

1.5.5 Programme co-ordinator/director

This should be a senior person who has had considerable experience in all aspects of ART. The programme co-ordinator/director should be able to co-

ordinate the activities of the rest of the team and take care of staff administrative matters, stock keeping, finance, maintenance of patient records, statutory requirements, and public relations. He/she should ensure that the staff are keeping up with the latest developments in their subject, by providing them with information from the literature, making available to them access to the latest journals, and encouraging them to participate in conferences and meetings and present their data. The programme co-ordinator/director should have a post-graduate degree in an appropriate medical or biological science. In addition, he/she must have a reasonable experience of ART.

1.6 ART Procedures

A variety of ART procedures have been described in the literature. Only those procedures that have been widely tested and proven to be satisfactory as of writing this document are listed here. It would be the responsibility of the National Accreditation Committee (Chapter 9) to ensure that the list given in this document is enlarged in real time as progress occurs in the field. It is hoped that the practitioners of ART in the country will bring to the notice of the Committee on a continuing basis, any new procedure for the practice of which there would appear to be a sound scientific case. The National Accreditation Committee or a body appointed by it will approve or disapprove the new procedure within six months of its having been made aware of in writing: if this is not done, the clinic could continue to use the procedure until the above body has taken a decision on it. No new procedure that has not been approved as above should be permitted to be used by an infertility clinic for more than the period mentioned above.

One of the primary concerns of all ART treatments is the safety of the patients and of their gametes and embryos which constitute the very beginning of a new individual's life. The basic tenets of any medical treatment mentioned in the Helsinki Declaration of 1964 and reiterated in October 2000 in Scotland (information available on the Internet) clearly spell out the ethical concerns of treating patients. These basic tenets are also applicable to ART. The clinic must ensure that a particular ART being offered is fully in consonance with the diagnosis made of the cause of infertility. More particularly, the clinic must make sure that patients are well informed about the treatment being offered to them, the reasons

of suggesting a particular form of treatment, and alternative therapies available if any.

If a clinic is offering an ART that is not listed in these guidelines now or as modified in the future (vide para 1 of this Section), the procedure must be approved by the clinics ethics committee (constituted as recommended by the ICMR ethical guidelines, 2000), justifying the need for the procedure and explaining why alternatives are not suitable. [Only clinics of Level 2 or Level 3 (Sections 2.5.3 and 2.5.4) would be required to have an ethics committee.] Informed consent from the patients would be mandatory in such cases as well. As mentioned in para one of this section, the clinic must also bring the new procedure to the notice of the National Accreditation Committee for its approval; if such an approval is not granted, all further use of the procedure must stop.

1.6.1 Artificial insemination with husband's semen (AIH)

The technique consists in placing in the interior of the vagina a sample of the unprocessed semen.

1.6.2 Artificial insemination with donor semen (AID)

The indications for AID are when there is (a) non-obstructive azoospermia; (b) the husband has a hereditary genetic defect; or (c) when the couples have Rh incompatibility.

The main advantage of AID is that it enables a couple to achieve pregnancy even though the husband is not the biological father. However, the possible transmission of diseases from the donor to the future child and the risk of consanguinity, constitute some drawbacks that must be brought to the notice of the patients. It is necessary to get the informed consent of both the partners after they are counselled about the possible psychological conflict they may face later in their life with the knowledge that one of them is not the biological parent of their child.

AID is an ethically acceptable procedure provided there is a medical indication and psychological confirmation for its use. Also, the normal

conditions of anonymity and screening of the donor must be met and only frozen sperm samples that have passed appropriate quarantining for infectious diseases such as HIV, hepatitis B and C, and syphilis should be used (for details see Chapter 3). AID involves the placing of a donor's semen into the interior of the vagina.

Common indications:

- © Husband has non-obstructive azoospermia.
- © Husband has a hereditary genetic defect.
- © The couple has Rh incompatibility.
- © The women is iso-immunized and has lost previous pregnancies and intrauterine transfusion is not possible.
- © Husband has severe oligozoospermia and the couple does not wish to undergo any of the sophisticated ART such as ICSI.

1.6.3 Intrauterine insemination with either husband's or donor semen (IUI-H or IUI-D)

IUI involves the processing of semen in the laboratory so as to yield pure, activated sperm, devoid of seminal plasma, which are then directly placed into the uterus.

Common indications:

- © Hostile uterine cervix that does not respond to medication. (Cervical hostility can readily be determined by carrying out proper tests such as the sperm-mucous interaction test or post-coital tests. Technical skills constitute an important factor in carrying out these tests correctly and reading the results.)
- © In cases where husband's sperm cannot be used for reasons as described above for AID.

1.6.4 *In vitro* fertilization and embryo transfer (IVF-ET)

The technique of IVF consists of bringing about the fertilization of the oocyte and the spermatozoa in the laboratory instead of in the woman's fallopian tube. IVF involves induction of ovulation in order to obtain multiple oocytes, thus making available more embryos with which higher pregnancy rates can be achieved. Serial determination of plasma estradiol levels and daily monitoring of ovarian follicular growth by ultrasonography would indicate the response to ovarian stimulation. At the appropriate moment of follicular growth, the follicles are aspirated to obtain the oocytes. The oocytes are mixed with appropriately capacitated spermatozoa from the husband (or the donor, if the medical condition indicates the use of donor sperm) and kept in an incubator for fertilization which is observed microscopically after 16 to 18 hours. Embryos are transferred into the uterine cavity between days 2 and 6 after oocyte aspiration. If implantation ensues, pregnancy can be confirmed by 14 to 16 days after embryo transfer by determining the presence of hCG in a blood or urine sample. Such a test is reliable only when progesterone is used for luteal supplementation instead of hCG.

The success rate of IVF is approximately one in every 4-5 women. IVF is the therapeutic option of reproductive medicine with the highest yield per attempt, coming close on many occasions to that achieved by fertile couples conceiving naturally.

Common indications:

© The original indication for IVF was irreversible pathology of the fallopian tubes, resulting from an inflammatory process or from previous surgery. However, in recent years the indications for IVF include infertility due to a subnormal male factor.

Other indications include:

© Idiopathic infertility.

© Endometriosis.

© Infertility of immunological origin.

1.6.5 IVF-associated techniques

Gamete Intrafallopian Tube Transfer (GIFT) or Tubal Embryo Transfer (TET) has been recommended for patients with undamaged fallopian tubes. Access to the tube is gained by laparoscopy or by retrograde catheterization through the uterine cervix. GIFT is associated with higher levels of pregnancy than IVF but it has the drawback that it is unable to demonstrate the fertilizing capacity of the gametes.

1.6.6 Intracytoplasmic sperm injection (ICSI) with ejaculated, epididymal or testicular spermatozoa

It is well known that the incidence of fertilization with sub-optimal semen is much lower in contrast to normal semen samples. It has been argued that since a sizeable number of couples are not suitable for IVF because their sperm count is far below 10 million/ml with less then 30% sperm being motile and more than 30% having abnormal morphology, alternate methods must be found to facilitate fertilization. Several approaches have been developed to circumvent the barriers (the zona pellucida and the ooplasmic membrane) that prevent the sperm reaching the ooplasm. Notable amongst these are: partial zona dissection (PZD), subzonal insemination (SUZI), and intracytoplasmic sperm injection (ICSI).

Live births have been reported using all these methods. The use of PZD or SUZI must be discouraged, as they do not offer any distinct advantage. ICSI is the most widely accepted choice of treatment for male factor infertility. ICSI can be carried out with fresh or frozen-thawed ejaculated or epididymal/ testicular motile or live spermatozoa.

1.6.6.1 Indications of ICSI with ejaculated spermatozoa

- Severe male-factor infertility.
- Fertilization failure after standard IVF treatment.

- Number of spermatozoa in the ejaculate too low for IVF.

1.6.6.2 Indications of ICSI with epididymal spermatozoa obtained by microsurgical epididymal sperm aspiration (MESA/PESA)

- Congenital bilateral absence of the vas deferens (CBAVD).
- Failed vasoepididymal anastomosis.
- Failed vasovasal anastomosis.
- Obstruction of both ejaculatory ducts.
- Anejaculation because of spinal cord injury.
- Retrograde ejaculation.

1.6.6.3 Indications of ICSI with testicular spermatozoa (TESA)

- Extensive scarring, rendering MESA/PESA impossible.
- Germ-cell hypoplasia (hypospermatogenesis).
- Germ-cell aplasia with focal spermatogenesis.
- Sertoli cell-only syndrome with focal spermatogenesis.

1.6.6.4 Indications of ICSI with *in vitro* matured oocytes

- Polycystic ovary.
- History of ovarian hyperstimulation.

1.6.7 Oocyte donation (OD) or embryo donation (ED)

Oocyte donation would necessitate using the husband's semen for fertilization and transferring the resultant embryo to the infertile female partner. Embryo donation would obviate the necessity of using the husband's semen. The choice of oocytes and embryos for oocyte or embryo donation would depend entirely on the circumstances prevalent at the time the infertile couple comes for treatment, and the access of the infertility clinic to frozen oocytes or embryos.

1.6.7.1 Indications for oocyte or embryo donation

- Gonadal dysgenesis.
- Premature ovarian failure.
- Iatrogenic (due to ovarian surgery or radiation, or chemical castration) ovarian failure.
- Women who have resistant ovary syndrome, or who are poor responders to ovulation induction.
- Women who are carriers of recessive autosomal disorders.
- Women who have attained menopause.

Donors should be healthy (as determined by medical and psychological examination, screening for STDs, and absence of HIV antibodies) women in the age group of 18-35 years. Oocytes may be obtained for donation, mostly by surgical intervention from women participating in an IVF program, or those undergoing elective sterilization or surgery.

The recipient should be a healthy woman (determined by medical and psychological examination) having normal genitalia (as determined by physical examination) and uterine cavity (as determined by hystero-salpingography). In case of OD, the semen characteristics of the husband must be determined to see if they are in conformity with those associated with normal fertility. The blood group of the donor should be noted; the donor should also be tested for antibodies to rubella, HIV, hepatitis, CMV, gonorrhea, syphilis, chlamydia, mycoplasma and trichomonas.

Ovum/embryo donation can be carried out in menopausal women with no surviving child and desiring to have a child. The endometrium of menopausal women has the ability to respond to sex hormones and provide a receptive environment for the implantation of an embryo.

Various protocols are now available to prepare the endometrium of the recipient for OD or ED with estrogens and progestogens until the placenta takes over the function of maintaining the gestation.

1.6.8 Cryopreservation

Facilities for cryopreservation are an essential component of an ART clinic as they are to be used under a variety of conditions such as those described below.

1.6.8.1 Freezing semen

Men, who are likely to suffer from psychological stress at the time of ovum pick-up or those who cannot be present at the time of ovum pick-up, are recommended to have their semen frozen for use at the appropriate time. One of the important reasons for freezing semen from donors is that any donor semen has to be quarantined for six months. The safety of using frozen sperm has been abundantly proven, both by experimental work and the actual results in humans. Matters of concern are the donor's health and the necessity to avoid donors who are infected with venereal diseases, hepatitis B or C, or HIV. One of the drawbacks of sperm freezing is an approximate 20 % loss in motility after thawing. Donors whose semen is frozen for future use are required to report to the semen bank six months after donation to be checked for HIV, HBV or HCV infection/disease status.

1.6.8.2 Freezing embryos

Embryos are routinely cryopreserved to enable storage of supernumerary embryos, as upto a maximum of only three embryos is allowed for transfer to avoid the risk of multiple pregnancies. Embryo freezing is a widespread routine procedure to increase cumulative pregnancy rates.

Human embryos can be successfully cryopreserved at any stage from zygote to blastocyst, using 1, 2 propanediol (PROH) or dimethylsulfoxide (DMSO) for zygotes and cleaved embryos and glycerol for blastocysts. The formation of ice crystals is of concern during embryo freezing. Using programmed, slow freezers reduces this problem considerably, and slow cooling is the most widely employed method. Human embryos are known to survive a simple ultra-rapid procedure of fast cooling but there is not much data on the efficacy of these techniques when used routinely. Straws or ampoules used for freezing embryos should be carefully and permanently labeled for identification purpose.

Patients should be fully informed before the treatment cycle on the procedure of cryopreservation, the risks and, particularly, what is to be done with their embryos if they do not use them. They should sign a consent form concerning the agreement for embryo freezing as well as for the future use of the embryos (also see Section 3.11).

When a serum supplementation is used in the preparation of freezing and thawing solutions, one must carefully avoid any risk of viral transmission to the embryo through the serum.

1.6.8.3 Oocyte cryopreservation

This procedure has been successfully used in cases where a large number of immature oocytes have been retrieved during ovum-pick-up. The oocyte can be thawed at a later date, matured *in vitro* and used for oocyte donation or similar procedures either on the person from whom the oocytes were retrieved or on other prospective recipients. However, the success rates in terms of fertilization, pregnancy and live births with the use of cryopreserved oocytes are not very encouraging. Much remains to be learnt on identifying the optimal stage of oocyte development when cryopreservation would be of value.

1.6.9 *In vitro* culture media

There has been a spurt of new media introduced for *in vitro* culture of gametes and embryos. If one takes a close look at these media, they are products that have evolved over the years. However, some manufacturers do not give the exact composition of their media but merely state that for reasons of patent protection or as trade secret they are constrained to give full details of the composition of their media (J D Biggers, Reproductive Biomedicine Online Vol. 1, No 3, 2000; also available on the world-wide web: rbmonline.com).

This is an undesirable situation. Infertility clinics that deal with human embryos and the future life of the products they create in the laboratory must be privy to the knowledge about the media they use, if need be by signing an

appropriate confidentiality agreement which would prohibit the clinic from using or passing on the proprietary information provided by the manufactures of the media to any other organisation that may commercially exploit this information.

When a serum supplementation has to be used in the preparation of media, one must carefully avoid the risk of viral transmission to the embryo through the serum.

1.6.10 The future ART technologies

Assisted reproductive technologies represent a rapidly progressing area in modern biology. It would be the responsibility of the National Accreditation Committee (Chapter 9) to ensure that this list of techniques is kept updated in real time.

1.6.11 Caution, precautions and concerns about ART practice

1.6.11.1 Ovarian stimulation

It is important that ART procedures aimed to facilitate the bringing together of oocytes and spermatozoa should occur when the oocyte is ready to fertilize. Under normal conditions it is very difficult to predict when ovulation will occur and whether the oocytes released will be fertilizable. It is, therefore, a common practice to induce follicular development by administering clomiphene citrate (CC) and or human menopausal gonadotropin (hMG) prepared from menopausal urine, followed by human chorionic gonadotropin (hCG) for the induction of ovulation just when the ovarian follicle has ripened and grown to its optimal size as determined by ultrasonography. Insemination can be carried out *in vivo*, or the oocyte aspirated and subjected to *in vitro* fertilization or ICSI. The time of oocyte maturation can be predicted by this method to facilitate carrying out the rest of the ART procedure.

Ovarian stimulation should be carried out with the utmost caution to avoid Ovarian Hyperstimulation Syndrome (OHSS). Basal blood levels of FSH and LH should be estimated on day 1 or 2 of the menstrual cycle. LH

levels twice as high as FSH are indicative of the woman having polycystic ovaries; such women are prone to develop multiple follicles when stimulated and also undergo OHSS. Oocytes aspirated from such ovaries usually fail to fertilize. If such women are subjected to mild ovarian stimulation with CC, it is important to carefully monitor their ovarian response ultrasonographically.

1.6.11.2 Indiscriminate use of ICSI

ICSI, one of the latest entrants to the field of ART, has been claimed to be a panacea for severe male infertility. This technique has never undergone critical evaluation in animal models before introducing it to treat human infertility. There are, therefore, some genuine concerns in regard to the use of ICSI; some of the fears underlying these concerns have come true (S. Oehninger and R. G. Gasolen: Should ICSI be the treatment of choice for all cases of *in vitro* conception ? No, not in light of the scientific data. Human Reproduction 17: 2337, 2002).

Although, ICSI has revolutionized the treatment for male infertility, its widespread use has raised medical concerns about the transfer of genetic defects to future generations. There is a higher than normal frequency of sex chromosome abnormalities in children born of ICSI procedures compared with the normal population (Science 281:651-652, 1988; Human Reproduction 13: 781-782,1998; Human Reproduction 16:115-120,2001; British Medical Journal 327: 852, 2003; Fertility and Sterility 80: 851, 2003). Besides, infertile men carrying Y chromosome microdeletions pass this defect to ICSI-born sons (Fertility and Sterility 74:909-915, 2000). During ICSI, the process of fertilization is dramatically changed. For example, there is no fertilization occurring *in vivo,* and the physiological maturation of sperm, its selection and penetration through oocyte investments, and its influence on embryonic spatial patterning (Nature 409: 517-521,2001), are bypassed. Because ICSI bypasses a part of the process of natural selection and certain early developmental mechanisms, concerns are expressed on the possible reproductive health risk(s) to the offspring.

In India, it is estimated that about 15% of married couples are sub-

fertile or infertile. Treatment of male-factor infertility in the country has improved dramatically with the introduction of ICSI, which is currently being practiced rather extensively in various major ART clinics in the country. It is, however, extremely important that this approach to treating male-factor infertility is carried out with caution, in view of the possible risk of vertically transmitting defective (spermatogenetic) fertility gene(s) to the male progeny, when the etiology of infertility is genetic in origin (Human Reproduction 13:219-227,1998). Thus, ICSI may fall below the general expectations of the Helsinki Declaration (WMA 1964 and 2000). ART clinics accredited under the present programme must therefore take due note of the above before resorting to ICSI, and counsel the couple for whom ICSI is being recommended, appropriately. Inspite of what has been said above, in some case, ICSI may still be the preferred choice of treatment for infertility.

1.6.11.3 Possible misuse of ART – sale of embryos and stem cells

There is a growing interest in embryonic stem cells because of their potential use for developing spare organs or replacing defective tissues such as parts of the brain destroyed due to Alzheimer's disease, or pancreatic cells in diabetic patients. The range of their potential use is limited only by one's imagination.

ART clinics are the only source of embryonic stem cells. Spare embryos are either frozen or returned to the infertile couple for replacement during a later cycle, or donated to another infertile couple, or discarded after five years using a suitable protocol (Section 3.11).

Recently, the USA banned all federal support for embryonic stem cell researches unless the laboratories could demonstrate that they had developed embryonic stem lines before August 10, 2001. However, private funding is allowed which encourages scientists in the USA to procure stem cells from abroad. Germany has banned all research on embryos produced in that country but permits the use of embryos brought from abroad.

The stand taken by the foreign governments on embryo research opens up the possibility of embryos from developing countries that do not have

appropriate national guidelines in this area, being commercially exploited and sold to foreign countries. Therefore sale or transfer of human embryos or any part thereof, or of gametes in any form and in any way – that is, directly or indirectly – to any party outside the country must be prohibited. Within the country, such embryos or gametes could be made available to bonafide researchers only as a gift, with both parties (the donor and the donee) having no commercial transaction, interest or intent.

Chapter 2

Screening of Patients for ART: Selection Criteria and Possible Complications

2.1 Patient Selection

During last two decades, there has been a marked increase in patient population in all infertility clinics the world over, but all infertility clinics may not be sufficiently equipped with the latest technology and expertise essential to offer the best possible help. Hence there is a need for patient selection, in order to categorise them in specific groups and then refer them to different levels of infertility care units for step-wise investigation and treatment.

Patient selection for referral and, finally, for ART should be based on the findings of basic investigations on the cause of infertility. These investigations should consist of the following.

2.1.1 Husband

- © Physical examination, both systemic and local, to detect any problem that might be the cause of infertility or that may modify the management of infertility.
- © Semen analysis including both morphological and functional tests; if any abnormality is detected, repeat tests should be done after suitable intervals. An abnormal finding on a repeat semen examination warrants full-scale investigation by an appropriate specialist to ascertain the cause and then institute the necessary treatment.
- © Screening for infections including syphilis, HBV, HCV and HIV, and their appropriate management.
- © If needed, appropriate endocrinological investigations and therapy.

2.1.2 Wife

- © Physical examination, both systemic and local, to detect any problem that might be the cause of infertility or that may modify the management of infertility.
- © Detection and timing of ovulation by basal body temperature (BBT), cervical mucus studies, ultrasonography, premenstrual endometrial biopsy, histopathological examination and serum progesterone estimation in the mid-luteal phase.

- © Assessment of tubal patency by appropriate investigations including hysterosalpingography, sonosalpingography, or laparoscopy if required, to find out/rule out specific problems and to select the appropriate therapy.
- © Screening for local factors including cervical mucus-related problems and lower genital tract infections, and instituting appropriate therapy.
- © Assessment of uterine cavity by hysteroscopy.
- © Screening for reproductive tract infections including syphilis, chlamydia, tuberculosis, HBV, HCV and HIV, and appropriate management.
- © If needed, appropriate endocrinological investigations and therapy.

Any gynaecologist not specifically trained in the subspeciality of infertility care can also complete these investigations.

Based on the results of these investigations, couples should be selected for treatment at different levels of infertility care units. Depending on the personnel competence and availability of facilities for investigation and treatment, there should be three levels of infertility care units: (a) primary infertility care units, (b) secondary infertility care units, and (c) tertiary infertility care units. These care units should work in a tier system.

2.2 Patient Selection for Treatment in Different Infertility Care Units

In general, infertile couples can be categorized broadly into three groups: (1) those with single defect in one of the partners; (2) those with multiple defects in one or both the partners; (3) no apparent defect in either partner (unexplained infertility).

2.2.1 Single defect in one of the partner

The fault may exist either in the male or in the female partner. The defect may be either treatable or untreatable. For example, in the female partner, a treatable defect could be tough or imperforate hymen, or oligo- or anovulation due to polycystic ovary syndrome or a sub-mucous fibroid. The untreatable female partner defects would include premature ovarian failure,

absence of uterus, dense pelvic adhesions due to endometriosis, tuberculosis, and pelvic inflammatory disease as a sequel to pelvic surgery.

Unlike female factor infertility, male factor infertility is seldom easily correctable. Except oligozoospermia without asthenospermia, and sexual dysfunction due to phimosis, no other male factor infertility is amenable to simple medical or surgical therapy.

If a single defect in one of the partners is correctable, approximately half of the patients will respond to conventional medical or surgical therapy and the other half will not. Further treatment for the unresponsive couples will then consist of counselling and an in-depth investigation, leading to the use of ART – failing which, adoption may be the only alternative.

For an uncorrectable single defect, either in the male or in the female partner, the choice would be between ART and adoption. The alternative to be chosen should be suggested by the counsellor after evaluation of the age, financial capabilities and psychological attitude of the couple.

2.2.2 Multiple defects in one or both partners

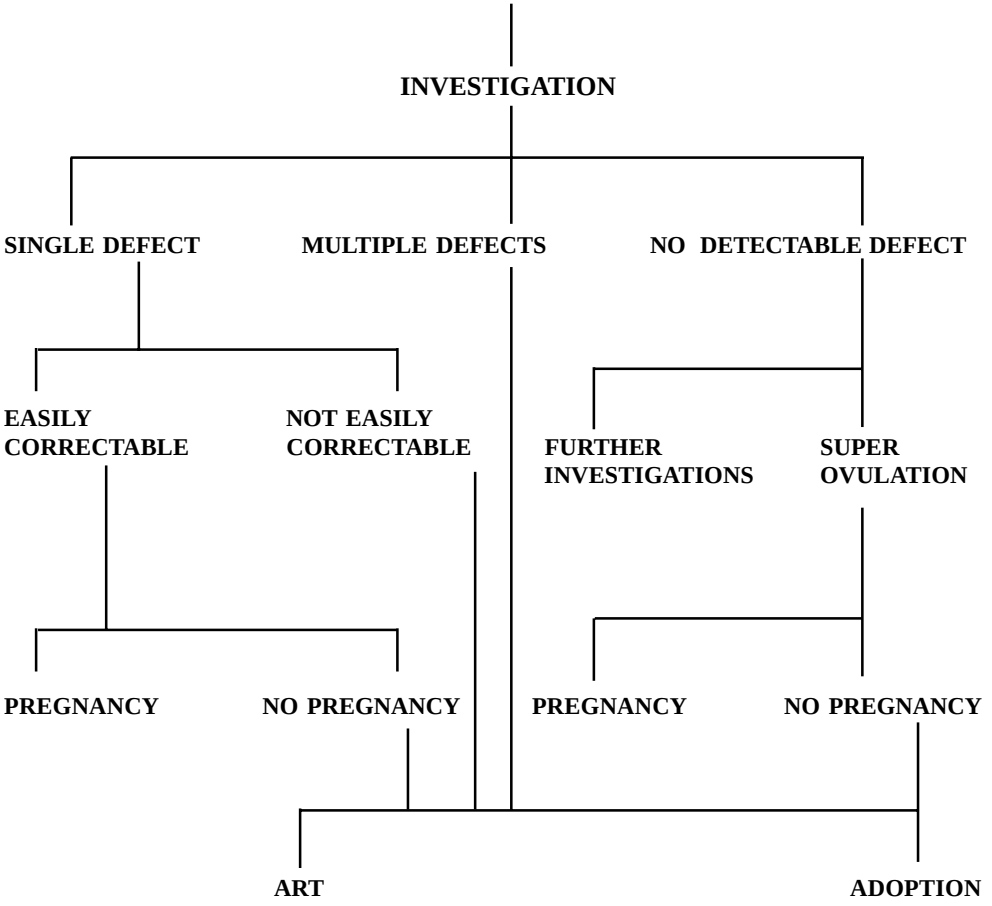
When multiple defects involve either one or both partners, attempt to correct these defects and hoping to achieve a pregnancy in the natural way is almost always unrewarding. This should be explained by the consulting gynaecologist/physician to the couple to prevent unnecessary expenditure by the couple. Judicious and effective counselling plays a very vital role under such circumstances; at least some couples will accept that at this point their treatment ends. A few will opt for adoption while others might wish to try the challenges of ART procedures.

2.2.3 No detectable defect in either partner (unexplained or idiopathic infertility)

This is a group most difficult to deal with as, they would have a right to ask that, in spite of everything being normal, what is standing in their way to achieve conception.

The approach to management protocol of infertile couples with regard to nature of defects may be summarized as follows:

OUTLINE OF MANAGEMENT PROTOCOL OF INFERTILE COUPLE:



2.3 Selection Criteria for ART

The choice of the procedure used, e.g. IVF-ET, GIFT, ZIFT, or ICSI, is made depending upon the needs, resources and circumstances of the couple, availability of the facilities, and experience and expertise of the gynaecologist/ embryologist. This section should be read in conjunction with Section 1.6.

2.3.1 Selection criteria for *in vitro* fertilization and embryo transfer (IVF-ET)

2.3.1.1 Tubal disease

IVF-ET can be offered where microsurgical techniques for tubal and peritoneal disease have failed or are unlikely to benefit the patient. The presence of peritubal adhesions, condition of the tubal wall, condition of the ciliary epithelium and degree of fimbrial damage would dictate the choice between IVF and microsurgery. Patients who have already undergone tuboplasty and those with inaccessible ovaries would be more suitable for IVF. In cases of history of ectopic pregnancy, IVF would be a better option.

2.3.1.2 Endometriosis

IVF is a suitable option for (a) women with moderate to severe endometriosis; (b) those in whom medical or surgical therapy has failed; and (c) sometimes in cases of mild to moderate endometriosis in the presence of other factors contributing to infertility.

2.3.1.3 Unexplained infertility

Couples who have prolonged unexplained infertility would benefit from IVF, as many factors such as subtle ovulation defects, defects in ovum pick-up, gamete transport, tubal environment, sperm abnormality, or oocyte abnormality may come to light when IVF is used.

2.3.1.4 Immunological factor

IVF can be used when there are antisperm antibodies either in the male or the female and when other techniques such as immunosuppression, use of condoms, intrauterine insemination and other therapeutic measures have failed.

2.3.1.5 Cervical factor

IVF can be offered for cervical factor only if repeated attempts (6 to 8 cycles) of intrauterine insemination have failed and other therapies have not resulted in pregnancy.

2.3.1.6 Male factor

IVF-ET is the logical therapy in cases of low concentrations of sperm (say, less than 10 million/ml), low motility (less than 30%), and/or abnormal sperm morphology (presence of > 60% abnormal forms). No universally accepted minimal sperm concentration for success in IVF exists. In cases of severe male factor infertility, assisted fertilization by means of micromanipulation and sperm injection (ICSI) can be offered even in obstructive and non-obstructive cases. In severe oligozoospermia, teratozoospermia, cryptozoospermia and azoospermia (obstructive/ nonobstructive), ICSI can be employed using either ejaculated or epididiymal sperm.

2.3.1.7 Ovarian disorders

IVF-ET can benefit patients with hypogonadotropic anovulation, oligoovulation, and luteal phase deficiency, although IVF is rarely indicated when these disorders exist as isolated conditions. IVF-ET can be used for women with luteinized unruptured follicle syndrome in polycystic ovarian disease.

2.3.1.8 Uterine disorders

Patients with Mullerian agenesis or congenital uterine anomalies, women with severe intrauterine adhesion refractory to surgical lysis of the adhesions, and hysterectomized patients can, through IVF, transfer their embryos to a surrogate mother.

2.3.1.9 In association with donor oocytes and donor embryos

Women who have undergone premature or timely menopause and women in the perimenopausal age group who do not show proper recruitment of follicles and who have other existing causes of infertility, can avail of the option of donor oocytes and donor embryos. Women with genetic disorders, those who have undergone radiation therapy, and those with ovaries that are not accessible by ultrasound due to severe adhesions, can also be advised to avail of donor oocytes for IVF-ET.

2.3.2 Selection criteria for gamete intra-fallopian transfer (GIFT)

The experimental background for GIFT is the ability of the fallopian tube to serve as the site for capacitation and fertilization in human beings. Earlier experiments using GIFT were carried out on monkeys that had undergone tubal resection and ligation. In 1979, Shettles reported pregnancy after intratubal transfer of freshly aspirated oocytes at the time of tubal re-anastomosis combined with cervical insemination. Asch and colleagues (1987) reported the first pregnancy and birth using laparoscopic GIFT. The indications for GIFT are almost similar to that for IVF-ET, except that GIFT cannot be performed on those who have both the fallopian tubes blocked.

2.3.3 Choosing between IVF-ET and GIFT

Decision in regard to which of these techniques should be utilized, must be individualized for each patient. The advantages of IVF over GIFT are documentation of fertilization, less trauma and relatively lower anaesthetic risk. There is no exposure to excess quantities of carbon dioxide in IVF as happens during laparoscopic insufflation with GIFT. On the other hand, GIFT is more

natural as fertilization occurs in the tubal ampulla, the gametes are minimally exposed *in vitro*, and early embryo development occurs in a natural environment.

2.3.4 Micro-assisted fertilization (SUZI and ICSI)

Subzonal insemination (SUZI), intracytoplasmic sperm injection (ICSI) and assisted hatching need micromanupulation of gametes. SUZI involves sperm injection in *in vitro*, in-to the sub zonal space of oocytes. This technique has now been virtually totally replaced by ICSI, which involves injection of sperm into the cytoplasm of the oocyte and which is useful in a variety of cases such as aging ova, elderly women, repeated failure of implantation in IVF, and in certain cases of male factor infertility. Assisted hatching of embryo by drilling a hole in the zona pellucida is resorted prior to embryo transfer for improving implantation rates.

2.4 Complications

ART procedures carry a small risk both to the mother and the offspring. These risks must be explained to the couple and appropriate counselling done. ART procedures are to be initiated only after patients understand these risks and still want to undergo ART. Some of the most commonly encountered risks are mentioned below (this list is not exhaustive).

2.4.1 Multiple gestation

The reported incidence of multiple gestation ranges from 20 to 30%. Incidence of twin pregnancies in the range of 10-20% may have to be accepted as inevitable, but specific efforts must be made to reduce the incidence of triplets and multiple births of higher order. Therefore, not more than three oocytes should be transferred for GIFT and not more than three embryos for IVF-ET at one sitting, excepting under exceptional circumstances (such as elderly women, poor implantation, advanced endometriosis or poor embryo quality; also see Section 3.5.13) which should be recorded; the remaining embryos, if any, may be cryopreserved and, if required, transferred at a later cycle.

2.4.2 Ectopic pregnancy

Ectopic pregnancy rates could be as high as up to 8% for ART procedures. The choice of an appropriate procedure as per guidelines mentioned earlier, especially in persons with tubal disease, may reduce the chances of an ectopic pregnancy.

2.4.3 Spontaneous abortion

Spontaneous abortion rates range from 20 to 35%. Abortion rates rise with increasing age of the mother and in multiple pregnancies, especially with three or more foetuses. In cases where more than two foetuses are present, selective embryo reduction should be advised. It is essential that the advantages of embryo reduction (better chances of the survival of other foetuses and the fact that they are likely to be born nearer term and with better birth weight) and disadvantages (the possibility that there might be an increased risk of abortion following the procedure) must be explained to the couple, and their informed consent taken before embryo reduction is attempted.

2.4.4 Preterm birth

There is a higher risk of premature/low birth weight delivery following ART, especially in the presence of multiple foetuses.

2.4.5 Ovarian hyperstimulation syndrome

The use of superovulation for ART entails a risk of hyperstimulation in some women, in the range of 0.2 to 8.0%. The extent of this risk is determined by the hormonal profile of the woman, the estradiol values (greater than 2500 pg/ml), the dose required for triggering ovulation, the ability to aspirate all the follicles at the time of oocyte retrieval, and several other factors. The programme director should be fully aware of the means to avoid hyperstimulation and also its treatment. Careful monitoring and management will reduce this risk as well as the morbidity associated with it.

In addition to these specific complications of ART, couples undergoing various ART procedures incur the risks associated with the operative and anaesthetic procedures involved in ART.

2.5 Categories of Infertility Care Units

The severity in the cause of infertility varies between couples. Sometimes, simple counselling or minor intervention will be all that is necessary. Others may require more aggressive treatment; such cases should be referred to speciality clinics. It is, therefore, recommended that infertility treatment should be offered at four levels. The infertility care units should be categorized into the four levels and authorized to offer treatments as described below. Patients should be referred by their gynaecologist or physician to whom they go first, if necessary, to the specific level of infertility care unit where appropriate facilities for investigation and treatment for that patient would be available. Level 1B, Level 2 and level 3 infertility clinics may encourage appropriately qualified gynaecologists of Level 1A clinics to use their facilities, provided the clinic thus being used by a gynaecologist takes the responsibility of ensuring that all norms stated in this document - including the maintenance of records - are followed.

2.5.1 Primary (Level 1A) infertility care units

These would be clinics where preliminary investigations are carried out and type and cause of infertility diagnosed. Primary infertility care unit or clinic could be a doctor's consulting room, such as a gynaecologist's or a physician's consulting room, or even a general hospital. Depending on the severity of infertility, the couple could be treated at the Level 1A clinic or referred to a speciality (Level 1B, Level 2 or Level 3) clinic.

Investigations into the cause of infertility by diligent history taking, physical examination and a simple semen analysis that can detect cases of azoospermia, can determine if the cause of infertility is related to the female or the male or to both the partners. Multifactorial or unexplainable cases should be referred to speciality secondary (Level 2) or tertiary (Level 3) infertility care units.

The gynaecologist or the physician in charge of a Level 1A infertility care unit should have an appropriate post-graduate degree and be capable of taking care of the above responsibilities.

The responsibilities of a Level 1A primary infertility care unit would be

1. Completion of the basic investigations mentioned above.
2. Treatment of minor anatomical defects like tough imperforate hymen. (Surgical perforation of hymen can be carried out after ensuring that the husband does not have erectile dysfunction. Extreme care must be taken in performing hymenectomy).
3. Treatment of mild endometriosis after confirming its presence by diagnostic laparoscopy carried out by a competent surgeon with adequate endoscopic experience.
4. Introduction of ovulation in non-ovulatory women (especially PCOS) with clomiphene citrate, with or without adjuncts like bromocriptine, eltroxin, dexamethasone or spironolactone. (Gonadotropin should not be used at a primary infertility care unit level).
5. Correcting minor endocrine disorders such as thyroid disorders or hyperprolactinemia, by prescribing appropriate corrective medications.
6. Treatment of oligozoospermia without asthenozoospermia.
7. Detecting infection of the reproductive tract using appropriate diagnostic tests, followed by normal health-care steps after carrying out appropriate antibiotic sensitivity tests. (Particular care must be taken to treat the couple and not the female or the male patient alone).
8. Ability to carry out AIH.
9. Ability to carry out IUI using processed semen of husband or donor obtained from an accredited laboratory or semen bank which must maintain a record (as in section 3.3.7) of complete details including the name, qualification and complete address of the gynaecologist/ clinic requesting the processed semen and carrying out the IUI.
10. Referral of the couple to Level 1B, Level 2 or Level 3 infertility care unit as appropriate, specially when the woman's age is more than 35, or when the couple has a multifactorial defect, or when

patients with single treatable defect have not responded to conventional therapy.

The gynaecologist or the physician in charge of a Level 1A infertility care unit should have an appropriate post-graduate degree or diploma, and be capable of taking care of the above responsibility. In case a Level 1A clinic is engaged in AIH and IUI it must maintain records (as in section 3.3.7) of the use of the requisitioned semen and of all AIH & IUI done, appropriately and confidentially; these records will be liable to inspection by an appropriate Review Committee (section 3.15). A Level 1A infertility care unit will not require an accreditation under these guidelines.

2.5.2 Primary (Level 1B) infertility care units engaging in IUI

These units would be required to have, in addition to what has been stated in Section 2.5.1, the facilities mentioned in the following two sub-sections (2.5.2.1 and 2.5.2.2). Infertility clinics falling into this category [like those of Level 2 and Level 3 (see the following sections)] shall need accreditation. The IUI in such clinics must be done under the supervision of a gynaecologist with a post-graduate degree.

2.5.2.1 Facilities for investigations:

i. Immunological tests for infertility, sperm cervical mucous penetration test (SCMPT), sperm cervical mucous test (SCMT), and test for antibodies (IgG, IgA) against sperm antigen in cervical mucous.
ii. Sperm function tests like hypo-osmotic swelling test (HOST), and assessment for improvement of sperm motility potential with pentoxifyllene co-culture.
iii. Assessment of follicular growth and ovulation by serial transvaginal sonography (TVS).
iv. Hysteroscopy, laparoscopy and transvaginal sonography.

2.5.2.2 Treatment facilities:

i. Facilities for semen preparation and certification and for intrauterine insemination (IUI), including an appropriate sterile area for IUI. (The facilities for investigation and for sperm preparation mentioned above could be shared with another accredited infertility clinic or semen bank).

2.5.3 Secondary (Level 2) infertility care units

These units must have infrastructure for further in-depth investigation and extended treatment of infertility except where oocytes are handled outside the body. Some of the investigations and treatment facilities required for Level 2 care units are detailed below:

2.5.3.1 Facilities for investigations:

i. Immunological tests for infertility, sperm cervical mucous penetration test (SCMPT), sperm cervical mucous test (SCMT), and tests for antibodies (IgG, IgA) against sperm antigen in cervical mucous.
ii. Sperm function tests like hypo-osmotic swelling test (HOST), and assessment of the improvement of sperm motility potential with pentoxifyllene co-culture.
iii. Assessment of follicular growth and ovulation by serial transvaginal sonography (TVS).
iv. Hysteroscopy, laparoscopy and transvaginal sonography.

2.5.3.2 Treatment facilities:

i. Facilities for semen preparation and intrauterine insemination (IUI).
ii. Provision for semen collection in men with a vibrator or an electroejaculator in functional erectile and ejaculatory problems.
iii. Conservative surgery either through a laparoscope, hysteroscope or via laparotomy. It should be possible to perform hysteroscopic cannulation of blocked tubes, and resection of submucous myoma or uterine septum.

iv. Combined medical-surgical therapy by a co-ordinated team as in endometriosis or in some cases of polycystic ovaries (ovarian drilling).
v. Provision for extended treatment of infertility except for oocyte pick up and IVF, ICSI etc.

2.5.4 Tertiary (Level 3) infertility care units

Such units will have three functions to perform, viz. diagnostic and therapeutic at the highest level of specialization and with the best of facilities, and research. Some examples of the first two functions are given below in Sections 2.5.4.1 to 2.5.4.3. If any of the facilities mentioned below does not exist in the clinic, the clinic should have access to such a facility in another appropriately accredited clinic, semen bank, or laboratory.

2.5.4.1 Diagnostic procedures for male infertility

i. Endocrine assay.
ii. Further tests for sperm function and integrity such as acrosome reaction and sperm-oocyte interaction *in vitro*.
iii. Assessment of cell contaminants, debris and infection.
iv. Karyotyping when sperm density, morphology and motility are abnormal.
v. Assessment of seminal plasma for viscosity, thinness, blood contamination and biochemical constituents.

2.5.4.2 Diagnostic procedures for female infertility

i. Endocrine assay.
ii. Karyotyping in premature ovarian failure in Kallman's syndrome.
iii. Colour Doppler for checking growing follicles, functional integrity of corpus luteum, and developing endometrium in stimulated or unstimulated cycle.
iv. GnRH challenge test in non-ovulation due to hypothalamic pituitary failure.
v. Clomiphene challenge tests to ascertain ovarian reserves before

ovulation induction or controlled ovarian hyperstimulation.

2.5.4.3 Therapeutic procedures

i. Induction of ovulation in refractory non-ovulation due to PCO-down regulation with a GnRH-agonist followed by induction with gonadotropin.
ii. All varieties of assisted reproductive technologies, including ICSI, mentioned earlier.
iii. Procedures for IUI using split ejaculate, pooled ejaculate or sperm recovered from post-coital specimen of urine in retrograde ejaculation.
iv. Embryo freezing.

Chapter 3

Code of Practice, Ethical Considerations and Legal Issues

3.1 Clinics which should be Registered

Clinics involved in any one of the following activities should be regulated, registered and supervised by the State Accreditation Authority/State Appropriate Authorities (Section 3.15).

1. Any treatment involving the use of gametes which have been donated or collected or processed *in vitro*, *except for* AIH, and for IUI by level 1A clinics who will not process the gametes themselves.
2. Any infertility treatment that involves the use and creation of embryos outside the body.
3. The processing or /and storage of gametes or embryos.
4. Research on human embryos.

The term ART clinic used in this document refers to a clinic involved in any one of the first three of the above activities.

3.2 Code of Practice

This Code of Practice deals with all aspects of the treatment provided and the research done at registered clinics. Those areas which most affect the doctors, scientists and patients and are a part of this code are summarized below.

3.2.1 Staff: A 'person responsible' shall take full responsibility for ensuring that the staff of the registered unit is sufficiently qualified, that proper equipment is used, that genetic material is kept and disposed off properly, and that the center complies with the conditions of its registeration. ***Guidelines for minimum standards*** and qualifications of clinical, scientific and counselling staffs are laid down in Chapter 1. Failure of the 'person responsible' to comply with the ***mandatory code of practice*** can lead to his/her removal or prosecution, or to the suspension of the clinic's registration.

3.2.2 Facilities: These must cover the standards expected in respect of provision of clinical, laboratory and counselling care mentioned in Chapters 1 and 2. Proper systems for monitoring and assessing practices and procedures are required to be in place (for example in the form of Standard Operating Procedures) in order to optimize the outcome of ART.

3.2.3 Confidentiality: Any information about clients and donors must be kept confidential. No information about the treatment of couples provided under a treatment agreement may be disclosed to anyone other than the accreditation authority or persons covered by the registration, except with the consent of the person(s) to whom the information relates, or in a medical emergency concerning the patient, or a court order. It is the above person's right to decide what information will be passed on and to whom, except in the case of a court order.

3.2.4 Information to patient: All relevant information must be given to the patient before a treatment is given. Thus, before starting treatment, information should be given to the patient on the limitations and results of the proposed treatment, possible side-effects, the techniques involved, comparison with other available treatments, the availability of counselling, the cost of the treatment, the rights of the child born through ART, and the need for the clinic to keep a register of the outcome of a treatment.

3.2.5 Consent: No treatment should be given without the written consent of the couple to all the possible stages of that treatment, including the possible freezing of supernumerary embryos. A standard consent form recommended by the accreditation authority should be used by all ART clinics. Specific consent must be obtained from couples who have their gametes or embryos frozen, in regard to what should be done with them if he/she dies, or becomes incapable of varying or revoking his or her consent.

3.2.6 Counselling: People seeking registered treatment must be given a suitable opportunity to receive proper counselling about the various implications of the treatment. No one is obliged to accept counselling but it is generally recognized as being beneficial, and couples should be encouraged to go

through it. The provision of facilities for counselling in an ART clinic (of Levels 1B, 2 or 3) is, therefore, mandatory. Couples should be referred for support or therapeutic counselling as appropriate.

3.2.7 Use of gametes and embryos: No more than three oocytes or embryos may be placed in a woman in any one cycle, regardless of the procedure/s used, excepting under exceptional circumstances (such as elderly women, poor implantation, adenomiosis, or poor embryo quality) which should be recorded. No woman should be treated with gametes or with embryos derived from the gametes of more than one man or woman during any one-treatment cycle.

3.2.8 Storage and handling of gametes and embryos: The 'highest possible standards' in the storage and handling of gametes and embryos in respect of their security, and in regard to their recording and identification, should be followed.

3.2.9 Research: The accreditation authority must approve all research that involves embryos created *in vitro*. A separate registration should be issued for each research project involving human embryos. The accreditation authority must not give a registation certificate unless it is satisfied that the use of human embryos is essential for the purposes of the proposed research and the research is in public interest.

Additionally:

(i) No human embryo may be placed in a non-human animal

(ii) All research projects must be approved by the Institutional Ethics Committee before submission to the accreditation authority.

3.2.10 Complaints: All registered ART clinics are required to have procedures for acknowledging and investigating complaints, and to have a nominated person to deal properly with such complaints. The accreditation authority must be informed of the number of complaints made in any year and those that are outstanding.

3.3 Responsibilities of the Clinic

3.3.1 To give adequate information to the patients (detailed in Section 3.4).

3.3.2 To explain to the patient the rationale of choosing a particular treatment (see Chapter 2) and indicate the choices the patient has (including the cheapest possible course of treatment), with advantages and disadvantages of each choice.

3.3.3 To help the patient exercise a choice, which may be best for him/her, taking into account the individual's circumstances.

3.3.4 To maintain records in an appropriate proforma (to be prescribed by the authority) to enable collation by a national body.

3.3.5 When commercial DNA fingerprinting becomes available, to keep on its record, if the ART clinic desires and couple agrees, DNA fingerprints of the donor, the child, the couple and the surrogate mother should be done.

3.3.6 To keep all information about donors, recipients and couples confidential and secure. The information about the donor (including a copy of the donor's DNA fingerprint if available, but excluding information on the name and address – that is, the individual's personal identity) should be released by the ART clinic after appropriate identification, only to the offspring and only if asked by him/her after he/she reaches the age of 18 years, or as and when specified and required for legal purposes, and never to the parents (excepting when directed by a court of law).

3.3.7 To maintain appropriate, detailed record of all donor oocytes, sperm or embryos used, the manner of their use (e.g. the technique in which they are used, and the individual/couple/surrogate mother on whom they are used). These records must be maintained for at least ten years after which the records must be transferred to a central depository to be maintained by the ICMR. If the ART clinic/centre is wound up during this period, the records must be transferred to the central repository in the ICMR.

3.3.8 To have the schedule of all its charges suitably displayed in the clinic and made known to the patient at the beginning of the treatment. There must be no extra charges beyond what was intimated to the patient at the beginning of the treatment.

3.3.9 To ensure that no technique is used on a patient for which demonstrated expertise does not exist with the staff of the clinic.

3.3.10 To be totally transparent in all its operations. The ART clinics must, therefore, let the patient know what the success rates of the clinic are in regard to the procedures intended to be used on the patient.

3.3.11 To have all consent forms available in English and local language(s).

3.4 Information and Counselling to be given to Patients

Information must be given to couples seeking treatment, on the following points:

3.4.1. The basis, limitations and possible outcome of the treatment proposed, variations in its effectiveness over time, including the success rates with the recommended treatments obtained in the clinic as well as around the world (this data should be available as a document with references, and updated every 6 – 12 months).

3.4.2. The possible side-effects (e.g. of the drug used) and the risks of treatment to the women and the resulting child, including (where relevant) the risks associated with multiple pregnancy.

3.4.3 The need to reduce the number of viable foetuses, in order to ensure the survival of at least two foetuses.

3.4.4. Possible disruption of the patient's domestic life which the treatment may cause.

3.4.5 The techniques involved, including (where relevant) the possible deterioration of gametes or embryos associated with storage, and possible pain and discomfort.

3.4.6 The cost (with suitable break-up) to the patient of the treatment proposed and of an alternative treatment, if any (there must be no other "hidden costs").

3.4.7 The importance of informing the clinic of the result of the pregnancy in a pre-paid envelope.

3.4.8 To make the couple aware, if relevant, that a child born through ART has a right to seek information (including a copy of the DNA fingerprint, if available) about his genetic parent/surrogate mother on reaching 18 years, excepting information on the name and address – that is, the individual's personal identity – of the gamete donor or the surrogate mother. The couple is not obliged to provide the information to which the child has a right, on their own to the child when he/ she reaches the age of 18, but no attempt must be made by the couple to hide this information from the child should an occasion arise when this issue becomes important for the child.

3.4.9 The advantages and disadvantages of continuing treatment after a certain number of attempts.

Pamphlets (one-page on each technique in all local languages and English) which give clear, precise and honest information about the procedure recommended to be used will help the couple make an informed choice.

3.5 Desirable Practices/Prohibited Scenarios

3.5.1 A third party donor of sperm or oocytes must be informed that the offspring will not know his/her identity. He/She must also be informed of the provisions in Section 3.4.8.

3.5.2 There would be no bar to the use of ART by a single women who wishes to have a child, and no ART clinic may refuse to offer its services to the above, provided other criteria mentioned in this document are satisfied. The child thus born will have all the legal rights on the woman or the man.

3.5.3 The ART clinic must not be a party to any commercial element in donor programmes or in gestational surrogacy.

3.5.4 A surrogate mother carrying a child biologically unrelated to her must register as a patient in her own name. While registering she must mention that she is a surrogate mother and provide all the necessary information about the genetic parents such as names, addresses, etc. She must not use/register in the name of the person for whom she is carrying the child, as this would pose legal issues, particularly in the untoward event of maternal death (in whose names will the hospital certify this death?). The birth certificate shall be in the name of the genetic parents. The clinic, however, must also provide a certificate to the genetic parents giving the name and address of the surrogate mother. All the expenses of the surrogate mother during the period of pregnancy and post-natal care relating to pregnancy should be borne by the couple seeking surrogacy. The surrogate mother would also be entitled to a monetary compensation from the couple for agreeing to act as a surrogate; the exact value of this compensation should be decided by discussion between the couple and the proposed surrogate mother. An oocyte donor can not act as a surrogate mother for the couple to whom the ooctye is being donated.

3.5.5 A third-party donor and a surrogate mother must relinquish in writing all parental rights concerning the offspring and vice versa.

3.5.6 No ART procedure shall be done without the spouse's consent.

3.5.7 The provision or otherwise of AIH or ART to an HIV-positive woman would be governed by the implications of the decision of the Supreme Court in the case of X – vs – Hospital 2 (1998) 8 Sec. 269 or any other relevant judgement of the Supreme Court, or law of the country, whichever is the latest.

3.5.8 Gametes produced by a person under the age of 21 shall not be used. The accepted age for a sperm donor shall be between 21 and 45 years and for the donor woman between 18 and 35 years.

3.5.9 Sex selection at any stage after fertilization, or abortion of foetus of any particular sex should not be permitted, except to avoid the risk of transmission of a genetic abnormality assessed through genetic testing of biological parents or through preimplantation genetic diagnosis (PGD).

3.5.10 No ART clinic shall offer to provide a couple with a child of the desired sex.

3.5.11 Collection of gametes from a dying person will only be permitted if the widow wishes to have a child.

3.5.12 No more than three eggs or embryos should be placed in a woman during any one treatment cycle, regardless of the procedure used, excepting under exceptional circumstances {such as elderly women (above 37 years), poor implantation (more than three previous failures), advanced endometriosis, or poor embryo quality} which should be recorded.

3.5.13 Use of sperm donated by a relative or a known friend of either the wife or the husband shall not be permitted. It will be the responsibility of the ART clinic to obtain sperm from appropriate banks; neither the clinic nor the couple shall have the right to know the donor identity and address, but both the clinic and the couple, however, shall have the right to have the fullest possible information from the semen bank on the donor such as height, weight, skin colour, educational qualification, profession, family background, freedom from any known diseases or carrier status (such as hepatitis B or AIDS), ethnic origin, and the DNA fingerprint (if possible), before accepting the donor semen. It will be the responsibility of the semen bank and the clinic to ensure that the couple does not come to know the identity of the donor. The ART clinic will be authorized to appropriately charge the couple for the semen provided and the tests done on the donor semen.

3.5.14 What has been said above under 3.5.13 also would be true of oocyte donation.

3.5.15 When DNA fingerprinting technology becomes commercially available, the ART clinic may offer to the couple, a DNA fingerprint of the donor

without revealing his/her identity, against appropriate payment towards the cost of the DNA fingerprint. An ART clinic will then have DNA fingerprinting done of the couple and keep the DNA fingerprints on its records.

3.5.16 Trans-species fertilization involving gametes of two species is prohibited.

3.5.17 Ova derived from foetuses cannot be used for IVF but may be used for research.

3.5.18 Semen from two individuals must never be mixed before use, under any circumstance.

3.5.19 Transfer of human embryo into a human male or into any animal belonging to any other species, must never be done and is prohibited.

3.5.20 The data of every accredited ART clinic must be accessible to an appropriate authority of the ICMR for collation at the national level.

3.5.21 Any publication or report resulting out of analysis of such data by the ICMR will have the concerned members of the staff of the ART clinic as co-authors.

3.5.22 The consent on the consent form must be a true informed consent witnessed by a person who is in no way associated with the clinic.

3.6 Requirements for a Sperm Donor

3.6.1 The individual must be free of HIV and hepatitis B and C infections, hypertension, diabetes, sexually transmitted diseases, and identifiable and common genetic disorders such as thalassemia.

3.6.2 The age of the donor must not be below 21 or above 45 years.

3.6.3 An analysis must be carried out on the semen of the individual, preferably using a semen analyzer, and the semen must be found to be normal according to WHO method manual for semen analysis, if intended to be used for ART.

3.6.4 The blood group and the Rh status of the individual must be determined and placed on record.

3.6.5 Other relevant information in respect of the donor, such as height, weight, age, educational qualifications, profession, colour of the skin and the eyes, record of major diseases including any psychiatric disorder, and the family background in respect of history of any familial disorder, must be recorded in an appropriate proforma.

3.7 Requirements for an Oocyte Donor

3.7.1 The individual must be free of HIV and hepatitis B and C infections, hypertension, diabetes, sexually transmitted diseases, and identifiable and common genetic disorders such as thalassemia.

3.7.2 The blood group and the Rh status of the individual must be determined and placed on record.

3.7.3 Other relevant information in respect of the donor, such as height, weight, age, educational qualifications, profession, colour of the skin and the eyes, and the family background in respect of history of any familial disorder, must be recorded in an appropriate proforma.

3.7.4 The age of the donor must not be less than 21 or more than 35 years.

3.8 Requirements for a Surrogate Mother

See Section 3.10.

3.9 How may Sperm and Oocyte Donors and Surrogate Mothers be Sourced?

3.9.1 Semen banks

3.9.1.1 Either an ART clinic or a law firm or any other suitable independent organization may set up a semen bank. If set up by an ART clinic it must operate as a separate identity.

3.9.1.2 The bank will ensure that all criteria mentioned in Section 3.6 (Requirements for a sperm donor) are met and a suitable record of all donors is kept for 10 years after which, or if the bank is wound up during this period, the records shall be transferred to an ICMR repository.

3.9.1.3 A bank may advertise suitably for semen donors who may be appropriately compensated financially.

3.9.1.4 On request for semen by an ART clinic, the bank will provide the clinic with a list of donors (without the name or the address but with a code number) giving all relevant details such as those mentioned in Section 3.6. The semen bank shall not supply semen of one donor for more than ten successful pregnancies. It will be the responsibility of the ART clinic or the patient, as appropriate, to inform the bank about a successful pregnancy. The bank shall keep a record of all semen received, stored and supplied, and details of the use of the semen of each donor. This record will be liable to be reviewed by the accreditation authority.

3.9.1.5 The bank must be run professionally and must have facilities for cryopreservation of semen, following internationally accepted protocols. Each bank will prepare its own SOP (Standard Operating Procedures) for cryopreservation.

3.9.1.6 Semen samples must be cryopreserved for at least six months before first use, at which time the semen donor must be tested for HIV and hepatitis B and C.

3.9.1.7 The bank must ensure confidentiality in regard to the identity of the semen donor.

3.9.1.8 A semen bank may store a semen preparation for exclusive use on the donor's wife or on any other woman designated by the donor. An appropriate charge may be levied by the bank for the storage. In the case of non-payment of the charges when the donor is alive, the bank would have the right to destroy the semen sample or give it to a bonafide organisation to be used only for research purposes. In the case of the death of the donor, the semen would become the property of the legal

heir or the nominee of the donor at the time the donor gives the sample for storage to the bank. All other conditions that apply to the donor would now apply to the legal heir, excepting that he cannot use it for having a woman of his choice inseminated by it. If after the death of the donor, there are no claimants, the bank would have the right to destroy the semen or give it to a bonafide research organisation to be used only for research purposes.

3.9.1.9 All semen banks will require accreditation.

3.9.2. Sourcing of oocytes and surrogate mothers

Law firms and semen banks will be encouraged to obtain (for example, through appropriate advertisement) and maintain information on possible oocyte donors and surrogate mothers as per details mentioned elsewhere in this document. The above organizations may appropriately charge the couple for providing an oocyte or a surrogate mother. The oocyte donor may be compensated suitably (e.g. financially) by the law firm or semen bank when the oocyte is donated. However, negotiations between a couple and the surrogate mother must be conducted independently between them.

3.9.3. Oocyte sharing

The system of oocyte sharing in which an indigent infertile couple that needs to raise resources for ART agrees to donate oocytes to an affluent infertile couple wherein the wife can carry a pregnancy through but cannot produce her own oocyte, for in-vitro fertilization with the sperm of the male partner of the affluent couple, for a monitory compensation that would take care of the expenses of an ART procedure on the indigent couple, must be encouraged.

3.10 Surrogacy: General Considerations

3.10.1 A child born through surrogacy must be adopted by the genetic (biological) parents unless they can establish through genetic (DNA) fingerprinting (of which the records will be maintained in the clinic) that the child is theirs.

3.10.2 Surrogacy by assisted conception should normally be considered only for patients for whom it would be physically or medically impossible/ undesirable to carry a baby to term.

3.10.3 Payments to surrogate mothers should cover all genuine expenses associated with the pregnancy. Documentary evidence of the financial arrangement for surrogacy must be available. The ART centre should not be involved in this monetary aspect.

3.10.4 Advertisements regarding surrogacy should not be made by the ART clinic. The responsibility of finding a surrogate mother, through advertisement or otherwise, should rest with the couple, or a semen bank (see 3.9.1.1; 3.9.2).

3.10.5 A surrogate mother should not be over 45 years of age. Before accepting a woman as a possible surrogate for a particular couple's child, the ART clinic must ensure (and put on record) that the woman satisfies all the testable criteria to go through a successful full-term pregnancy.

3.10.6 A relative, a known person, as well as a person unknown to the couple may act as a surrogate mother for the couple. In the case of a relative acting as a surrogate, the relative should belong to the same generation as the women desiring the surrogate.

3.10.7 A prospective surrogate mother must be tested for HIV and shown to be seronegative for this virus just before embryo transfer. She must also provide a written certificate that (a) she has not had a drug intravenously administered into her through a shared syringe, (b) she has not undergone blood transfusion; and (c) she and her husband (to the best of her/his knowledge) has had no extramarital relationship in the last six months. (This is to ensure that the person would not come up with symptoms of HIV infection during the period of surrogacy.) The prospective surrogate mother must also declare that she will not use drugs intravenously, and not undergo blood transfusion excepting of blood obtained through a certified blood bank.

3.10.8 No woman may act as a surrogate more then thrice in her lifetime.

3.11 Preservation, Utilization & Destruction of Embryos

3.11.1 Couples must give specific consent to storage and use of their embryos. The Human Fertilization & Embryology Act, UK (1990), allows a 5-year storage period which India would also follow.

3.11.2 Consent shall need to be taken from the couple for the use of their stored embryos by other couples or for research, in the event of their embryos not being used by themselves. This consent will not be required if the couple defaults in payment of maintenance charges after two reminders sent by registered post.

3.11.3 Research on embryos shall be restricted to the first fourteen days only and will be conducted only with the permission of the owner of the embryos.

3.11.4 No commercial transaction will be allowed for the use of embryos for research.

3.12 Rights of a Child Born through various ART Technologies

3.12.1 A child born through ART shall be presumed to be the legitimate child of the couple, having been born in wedlock and with the consent of both the spouses. Therefore, the child shall have a legal right to parental support, inheritance, and all other privileges of a child born to a couple through sexual intercourse.

3.12.2 Children born through the use of donor gametes, and their "adopted" parents shall have a right to available medical or genetic information about the genetic parents that may be relevant to the child's health.

3.12.3 Children born through the use of donor gametes shall not have any right whatsoever to know the identity (such as name, address, parentage, etc.) of their genetic parent(s). A child thus born will, however, be provided all other information (including that mentioned in Section 3.4.8)

about the donor as and when desired by the child, when the child becomes an adult. While the couple will not be obliged to provide the above "other" information to the child on their own, no deliberate attempt will be made by the couple or others concerned to hide this information from the child as and when asked for by the child.

3.12.4 In the case of a divorce during the gestation period, if the offspring is of a donor programme – be it sperm or ova – the law of the land as pertaining to a normal conception would apply.

3.13 Responsibilities of the Drug Industry

3.13.1 Drug companies must not make exaggerated claims for infertility drugs and market them only to qualified specialists. All available information on the drug must be provided to the specialist.

3.13.2 Infertility drugs must be sold only on prescription by a qualified doctor/ ART specialist.

3.13.3 There has been a spurt of new media introduced for *in vitro* culture of gametes and embryos. Companies dealing with culture media do not give full details of the composition because they wish to retain this as a trade secret. This poses problems for those dealing with human embryos. The future life of the products created in the laboratory is dependant, to a certain extent, on the culture media used. ART centers should not encourage companies that do not give details of the full composition of the culture media. This will also make it possible to take legal action against a company supplying something different from what it is stated to be.

3.14 General Considerations

3.14.1 Minimum age for ART:

For a woman between 20 and 30 years, two years of cohabitation/ marriage without the use of a contraceptive, excepting in cases where the man is infertile or the woman cannot physiologically conceive. For a

woman over 30 years, one year of cohabitation/marriage without use of contraceptives. Normally, no ART procedure shall be used on a woman below 20 years.

3.14.2 Advertisements of an infertility centre:

False claims via hoardings and paper advertisements are a cheap way of attracting a clientele that is vulnerable and, therefore, easily swayed. Such advertisements shall be banned. An honest display at appropriate places or publicity of statistics, fee structure, quality of service and of service provided, will be encouraged, provided the guidelines laid down by the Medical Council of India in this regard, are not violated.

3.14.3 As already mentioned, sperm banks where a complete assessment of the donor has been done, medical and other vital information stored, quality of preservation ensured, confidentiality assured, and strict control exercised by a regulatory body, must be set up. Donor sperm would be made available only through such specialized banks/centers.

3.14.4 In the light of a recent technological breakthrough where a fertilized ovum containing ooplasm (including mitochondria) from a donor ovum has been successfully cultured, the embryo or the future child may now have three genetic parents. In such cases, the ooplasm donor must sign a waiver relinquishing all rights on the child, and must be screened for and declared free of known mitochondrial genetic abnormalities.

3.14.5 No new ART clinic may start operating unless it has obtained a temporary registration to do so. This registration would be confirmed only if the clinic obtains accreditation (permanent registration) from the Center or State's appropriate accreditation authority within two years of obtaining the temporary registration. The registration must be renewed every seven years.

3.14.6 Existing ART clinics must obtain a temporary registration within six months of the notification of the accreditation authority, and appropriate accreditation (permanent registration) within two years of the notification.

3.14.7 The Center/State Government would close down any unregistered clinic not satisfying the above criteria.

3.14.8 If the ART clinic that has applied for a temporary registration to the appropriate accreditation authority, does not receive the registration (or a reply) within two months of the receipt of the application from the concerned office of the authority, the ART clinic would be deemed to have received the registration. The same would apply for the permanent registration after the above-prescribed period.

3.14.9 As pointed out in section 1.6.12.2, the technique of ICSI has never undergone critical testing in animal models, but was introduced into the human situation directly. Defects in spermatogenesis and sperm production can be often traced to genetic defects. Such individuals are normally prevented from transmitting these defects to their offspring because of their natural infertility. ICSI by–passes this barrier and may help in transmitting such defects to the offspring, which sometimes may be exaggerated in the offspring. In view of this, the ART clinic must point out to the prospective parents that their child born through ICSI may have a slightly higher risk over and above the normal risk, of suffering from a genetic disorder.

3.14.10 Human cloning for delivering replicas must be banned.

3.14.11 Stem cell cloning and research on embryos (less than 15 days old) needs to be encouraged.

3.14.12 All the equipments/machines should be calibrated regularly.

3.15 Responsibilities of the Accreditation Authority

A State Accreditation Authority will be set up by the State Governments through its Department of Health and/or Family Welfare to oversee all policy matters relating to Accreditation, Supervision and Regulation of ART Clinics in the States in accordance with the National Guidelines. The State Government may also set up appropriate authorities for implementation of the Guidelines for the whole or a part of State having regard to the number of the ART Clinics. The

appropriate authority would have right to visit individually or collectively, any ART Clinic/Centre(s) accredited or not accredited, once a year with or without prior information to the clinic/center, to determine if the ethical guidelines and operative procedures mentioned here are being followed. If not, the appropriate authority will point out the lapses to the clinic/center in writing. If these lapses continued for a maximum period of six months (during which period the clinic shall not engage in any activity related to the lapses), the appropriate authority would recommend to the State Accreditation Authority that the clinic/center may be ordered to be closed. The State Accreditation Authority will have the powers to order the closing of such a clinic or a center. The appropriate authority may be delegated powers to impose a fine or a penalty on the center/clinic. The above-mentioned appropriate authority would consist of appropriately qualified scientists, technologists and sociologists. The appropriate authority will also be authorized to visit and regulate semen banks in the manner mentioned above. In addition to the above, the Ministry of Health and Family Welfare, Govt. of India, will set up a National Advisory Committee. The National Advisory Committee may be headed by the Secretary, Health and Family Welfare as chairman and the Director General of ICMR as co-chairman. The National Advisory Committee will advise the Central Government on policy matters relating to regulation of ART Clinics. Composition of the Committee is given in Chapter 9.

The State Accreditation Authority will have the rights and the responsibility of fixing the upper limit of charges for gamete donation and surrogacy and of revising these charges from time to time.

3.16 Legal Issues

3.16.1 Legitimacy of the child born through ART

A child born through ART shall be presumed to be the legitimate child of the couple, born within wedlock, with consent of both the spouses, and with all the attendant rights of parentage, support and inheritance. Sperm/oocyte donors shall have no parental right or duties in relation to the child, and their anonymity shall be protected except in regard to what is mentioned under item 3.12.3.

3.16.2 Adultery in the case of ART

ART used for married woman with the consent of the husband does not amount to adultery on part of the wife or the donor. AID without the husband's consent can, however, be a ground for divorce or judicial separation.

3.16.3 Consummation of marriage in case of AIH

Conception of the wife through AIH does not necessarily amount to consummation of marriage and a decree of nullity may still be granted in favor of the wife on the ground of impotency of the husband or his willful refusal to consummate the marriage. However, such a decree could be excluded on the grounds of approbation.

3.16.4 Rights of an unmarried woman to AID

There is no legal bar on an unmarried woman going for AID. A child born to a single woman through AID would be deemed to be legitimate. However, AID should normally be performed only on a married woman and that, too, with the written consent of her husband, as a two-parent family would be always better for the child than a single parent one, and the child's interests must outweigh all other interests.

3.16.5 Posthumous AIH through a sperm bank

Though the Indian Evidence Act, 1872, says that a child born within 280 days after dissolution of marriage (by death or divorce) is a legitimate child since that is considered to be the gestation period, it is pertinent to note that this Act was enacted as far back as 1872 when one could not even visualize ART. The law needs to take note of the scientific advancements since that time. Thus a child born to a woman artificially inseminated with the stored sperms of her deceased husband must be considered to be a legitimate child notwithstanding the existing law of presumptions under our Evidence Act. The law needs to move alongwith medical advancements and suitably amended so that it does not give rise to dilemma or unwarranted harsh situations.

3.17 Institutional Ethics Committees

Each ART clinic of Levels 1B, 2 and Level 3 must have its own ethics committee constituted according to ICMR Guidelines, comprising reputed ART practitioners, scientists who are knowledgeable in developmental biology or in clinical embryology, a social scientist, a member of the judiciary and a person who is well-versed in comparative theology. Should the local ART clinic have difficulty in establishing such a body, the state accreditation authority should constitute such a body, co-opting a representative of the ART clinic.

Chapter 4

Sample Consent Forms

4.1 Consent Form to be signed by the Couple

We have requested the Centre (named above) to provide us with treatment services to help us bear a child.

We understand and accept (as applicable) that:

1. The drugs that are used to stimulate the ovaries to raise oocytes have temporary side effects like nausea, headaches and abdominal bloating. Only in a small proportion of cases, a condition called ovarian hyper-stimulation occurs, where there is an exaggerated ovarian response. Such cases can be identified ahead of time but only to a limited extent. Further, at times the ovarian response is poor or absent, in spite of using a high dose of drugs. Under these circumstances, the treatment cycle will be cancelled.

2. There is no guarantee that:

   a. The oocytes will be retrieved in all cases.

   b. The oocytes will be fertilized.

   c. Even if there were fertilization, the resulting embryos would be of suitable quality to be transferred.

   All these unforeseen situations will result in the cancellation of any treatment.

3. There is no certainty that a pregnancy will result from these procedures even in cases where good quality embryos are replaced.

4. Medical and scientific staff can give no assurance that any pregnancy will result in the delivery of a normal living child.

5. **Endorsement by the ART clinic**

   I/we have personally explained to _____ and _____ the details and implications of his/her/their signing this consent/approval form, and made sure to the extent humanly possible that he/she/they understand these details and implications.

6. This consent would hold good for all the cycles performed at the clinic.

Name and Signature of the Husband

Name and Signature of the Wife

Name, Address and Signature of the Witness from the clinic

Name and Signature of the Doctor

Dated:

4.2 Consent for Artificial Insemination with Husband's Semen

_____and_____
_____, being husband and wife and both of legal age, authorize Dr._____ to inseminate the wife artificially with the semen of the husband for achieving conception.

We understand that even though the insemination may be repeated as often as recommended by the doctor, there is no guarantee or assurance that pregnancy or a live birth will result.

We have also been told that the outcome of pregnancy may not be the same as those of the general pregnant population, for example in respect of abortion, multiple pregnancies, anomalies or complications of pregnancy or delivery.

The procedure(s) carried out does (do) not ensure a positive result, nor do they guarantee a mentally and physically normal body. This consent holds good for all the cycles performed at the clinic.

Endorsement by the ART clinic

I/we have personally explained to _____ and _____ the details and implications of his/her/their signing this consent/approval form, and made sure to the extent humanly possible that he/she/they understand these details and implications.

Name, Address and Signature of the Witness from the clinic

Signed: _____ (Husband)
_____ (Wife)

Name and Signature of the Doctor

Dated:

4.3 Consent for Artificial Insemination with Donor Semen

We, _____ and _____, being husband and wife and both of legal age, authorize Dr._____ to inseminate the wife artificially with semen of a donor (registration no._____; obtained from _____ semen bank) for achieving conception.

We understand that even though the insemination may be repeated as often as recommended by the doctor, there is no guarantee or assurance that pregnancy or a live birth will result.

We have also been told that the outcome of pregnancy may not be the same as those of the general pregnant population, for example in respect of abortion, multiple pregnancies, anomalies or complications of pregnancy or delivery.

We declare that we shall not attempt to find out the identity of the donor.

I, the husband, also declare that should my wife bear any child or children as a result of such insemination (s), such child or children shall be as my own and shall be my legal heir (s).

The procedure(s) carried out does (do) not ensure a positive result, nor do they guarantee a mentally and physically normal body. This consent holds good for all the cycles performed at the clinic.

Endorsement by the ART clinic

I/we have personally explained to _____and _____ the details and implications of his/her/their signing this consent/approval form, and made sure to the extent humanly possible that he/she/they understand these details and implications.

Name, Address and Signature
of the Witness from the clinic

Signed: _____
(Husband)
(Wife) _____

Name and Signature of the Doctor

Dated:

4.4 Consent for Freezing of Embryos

We _____ and _____ consent to freezing of the embryos that have resulted out of IVF/ICSI with our gametes. We understand that the embryos would be normally kept frozen for five years. If we wish to extend this period, we would let you (the ART clinic) know at least six months ahead of time. If you do not hear from us before that time, you will be free to (a) use the embryos for a third party; (b) use them for research purposes; or (c) dispose them off. We also understand that some of the embryos may not survive the subsequent thaw and that frozen embryo-replaced cycles have a lower pregnancy rate than when fresh embryos are transferred.

*Husband

In the unforeseen event of my death, I would like

The embryos to perish	☐
To be donated to my wife	☐
To be donated to a third party	☐
Used for research purposes	☐

Signed: Dated:

***Wife**

In the unforeseen event of my death, I would like

The embryos to perish	☐
To be donated to my husband	☐
To be donated to a third party	☐
Used for research purposes	☐

Signed Dated :

Endorsement by the ART clinic

I/we have personally explained to _____ and _____the details and implication of his/her/their signing this consent/approval form, and made sure to the extent humanly possible that he/she/they understand these details and implications.

Name, Address and Signature of the Witness from the clinic

Name and Signature of the Doctor Dated

* The appropriate option may be ticked

4.5 Consent for the Procedure of PESA and TESA

Name of female partner
Name of male partner

We hereby request and give consent to the procedure of PESA and TESA for ICSI, to be performed on the male partner.

We understand that

a) There is no guarantee that the sperm will be successfully removed or that sperm will necessarily fertilise our oocytes.

b) Should the sperm retrieval fail, the following options will be available for the retrieved oocytes.

i) Insemination of all or some oocytes using donor sperm ☐

ii) Donation of oocytes to another infertile couple ☐

iii) Disposal of oocytes according to the ethical guidelines ☐

(Tick the appropriate option)

Each of the above points has been explained to us by _____

The procedure(s) carried out does (do) not ensure a positive result, nor do they guarantee a mentally and physically normal body. This consent holds good for all the cycles performed at the clinic.

Endorsement by the ART clinic

I/we have personally explained to _____ and _____ the details and implications of his/her/their signing this consent/approval form, and made sure to the extent humanly possible that he/she/they understand these details and implications.

Signature of Male Partner

Signature of Female Partner

Name, Address and Signature of the Witness from the clinic

Name and Signature of the Doctor

Dated

4.6 Consent for Oocyte Retrieval/Embryo Transfer

Woman's Name:

Woman's Address:
Name of the Clinic:

I have asked the Clinic named above to provide me with treatment services to help me bear a child. I consent to:

a) Being prepared for oocyte retrieval by the administration of hormones and other drugs

b) The removal of oocytes from my ovaries under ultrasound guidance/ laparoscopy

c) The mixing of the following:

☐ My oocytes ☐ the sperm of my husband

☐ Anonymous donor oocyte ☐ anonymous donor sperm

(Tick the appropriate and strike off the others)

d) the placing in my _____ of

e) 1. _____ (no) of the oocytes mixed with the sperm

f) 2. _____ (no) of the resulting embryos

g) 3. _____ (no) of our cryo-preserved embryos

h) 4. _____ (no) of embryo (s) obtained anonymously

I had a full discussion with _____ about the above procedures and I have been given oral and written information about them.

I have been given a suitable opportunity to take part in counselling about the implications of the proposed treatment.

The type of anaesthetic proposed (general/regional/sedation) has been discussed in terms which I have understood.

Endorsement by the ART clinic

I/we have personally explained to _____ and _____ the details and implications of his/her/their signing this consent/approval form, and made sure to the extent humanly possible that he/she/they understand these details and implications.

Signature of Female Partner

Name, Address and Signature
of the Witness from the clinic

Name and Signature of the Doctor

Dated

4.6.1 Consent of Husband

As the husband, I consent to the course of the treatment outlined above. I understand that I will become the legal father of any resulting child, and that the child will have all the normal legal rights on me.

Name, Address & Signature : _____
(Husband)

Name, Address and Signature
of the witness from the clinic: _____

Name and Signature of the Doctor: _____

Dated

4.7 Agreement for Surrogacy

I, _____ (the woman), with the consent of my husband (name), of _____ (address) have agreed to act as a host mother for the couple, _____ _____ (wife) and _____ (husband), both of whom are unable (or do not wish to) to have a child by any other means.

I had a full discussion with _____of the clinic on _____ in regard to the matter of my acting as a surrogate mother for the child of the above couple.

I understand that the methods of treatment may include:

1. Stimulation of the genetic mother for follicular recruitment
2. The recovery of one or more oocytes from the genetic mother by ultrasound-guided oocyte recovery or by laparoscopy.
3. The fertilisation of the oocytes from the genetic mother with the sperm of her husband or an anonymous donor.
4. The fertilisation of a donor oocyte by the sperm of the husband.
5. The maintenance and storage by cryopreservation of the embryo resulting from such fertilisation until, in the view of the medical and scientific staff, it is ready for transfer.
6. Implantation of the embryo obtained through any of the above possibilities into my uterus, after the necessary treatment if any.

I have been assured that the genetic mother and the genetic father have been screened for HIV and hepatitis B and C before oocyte recovery and found to be seronegative for all these diseases. I have, however, been also informed that there is a small risk of the mother or/and the father becoming seropositive for HIV during the window period.

I consent to the above procedures and to the administration of such drugs that may be necessary to assist in preparing my uterus for embryos transfer, and for support in the luteal phase.

I understand and accept that there is no certainty that a pregnancy will result from these procedures.

I understand and accept that the medical and scientific staff can give no assurance that any pregnancy will result in the delivery of a normal and living child.

I am unrelated/related (relation) _____ to the couple (the would be genetic parents).

I have worked out the financial terms and conditions of the surrogacy with the couple in writing and an appropriately authenticated copy of the agreement has been filed with the clinic, which the clinic will keep confidential.

I agree to hand over the child to _____ and _____ , the couple (to _____ in case of their separation during my pregnancy, or to the survivor in case of the death of one of them during pregnancy) as soon as I am permitted to do so by the Hospital/Clinic/Nursing home where the child is delivered.

I undertake to inform the ART clinic, _____, of the result of the pregnancy.

I take no responsibility that the child delivered by me will be normal in all respects. I understand that the biological parents of the child have a legal obligation to accept their child that I deliver and that the child would have all the inheritance rights of a child of the biological parents as per the prevailing law.

I will not be asked to go through sex determination tests for the child during the pregnancy and that I have the full right to refuse such tests.

I understand that I would have the right to terminate the pregnancy at my will; I will then refund all certified and documented expenses incurred on the pregnancy by the biological parents or their representative. If, however, the pregnancy has to be terminated on expert medical advice, these expenses will not be refunded.

I have been tested for HIV, hepatitis B and C and shown to be seronegative for these viruses just before embryo transfer.

I certify that (a) I have not had any drug intravenously administered into me through a shared syringe; (b) I have not undergone blood transfusion; and (c) I and my husband have had no extramarital relationship in the last six months.

I also declare that I will not use drugs intravenously, undergo blood transfusion excepting of blood obtained through a certified blood bank, and avoid sexual intercourse during the pregnancy.

I undertake not to disclose the identity of the couple.

In the case of the death of both the husband and wife (the couple) during my pregnancy, I will deliver the child to _____ or _____ in this order; I will be provided, before the embryo transfer into me, a written agreement of the above persons to accept the child in the case of the above-mentioned eventuality.

Endorsement by the ART clinic

I/we have personally explained to _____ and _____ the details and implications of his/her/their signing this consent/approval form, and made sure to the extent humanly possible that he/she/they understand these details and implications.

Signed:
(Surrogate Mother)

Name, Address and Signature
of the Witness from the clinic

Name and Signature of the Doctor

Dated

4.8 Consent Form for the Donor of Eggs

I Ms. _____ consent to donate my eggs to couples who are unable to have a child by other means.

I have had a full discussion with Dr. _____ (name and address of the clinician) on _____.

I have been counselled by _____ (name and address of independent counsellor) on _____.

I understand that there will be no direct or indirect contact between me and the recipient, and my personal identity will not be disclosed to the recipient or to the child born through the use of my gamete.

I understand that I shall have no rights whatsoever on the resulting offspring and vice versa.

I understand that the method of treatment may include:

- Stimulating my ovaries for multifollicular development.
- The recovery of one or more of my eggs under ultrasound-guidance or by laparoscopy under sedation or general anesthesia.
- The fertilization of my oocytes with recipient's husband's or donor sperm and transferring the resulting embryo into the recipient.

Endorsement by the ART clinic/oocyte bank

I/we have personally explained to _____ and _____ the details and implications of his/her/their signing this consent/approval form, and made sure to the extent humanly possible that he/she/they understand these details and implications.

Signed: _____

Name, Address and Signature of the Witness from the clinic

Name and Signature of the Doctor

Dated

4.9 Consent Form for the Donor of Sperm

I Mr. _____ consent to donate my sperm to couples who are unable to have a child by other means.

I have had a full discussion with Dr. _____ (name and address of the clinician) on _____.

I have been counselled by _____ (name and address of independent counsellor) on _____.

I understand that there will be no direct or indirect contact between the recipient, and me and my personal identity will not be disclosed to the recipient or to the child born through the use of my gamete.

I understand that I shall have no rights whatsoever on the resulting offspring and vice versa.

Endorsement by the ART clinic/semen bank

I/we have personally explained to _____ and _____ the details and implications of his/her/their signing this consent/approval form, and made sure to the extent humanly possible that he/she/they understand these details and implications.

Signed: _____

Name, Address and Signature
of the Witness from the clinic

Name and Signature of the Doctor Dated

Chapter 5

Training

5 Training

ART necessitates that the laboratory staff must have basic knowledge of mammalian embryology, reproductive endocrinology, genetics, biochemistry, molecular biology, microbiology, and *in vitro* culture techniques. The laboratory staff must also be knowledgeable in the subjects practiced by the clinician. The clinical staff must be well-versed in reproductive endocrinology, pathology, endoscopy, ultrasonography, gynaecology and/or andrology. The clinician must be knowledgeable about the importance of the procedures used in the embryology laboratory. It is only through an understanding of the basic principles of the several disciplines involved that an integrated team can be put in place to make a successful ART clinic.

ART does not form a part of the medical curriculum anywhere in India although the number (10 – 15% of the adult population in the reproductive age group) of infertile couples needing ART is quite large. There is, therefore, a need to institute training programes in ART. Such training can best be imparted in a teaching institution, which has all the branches of the basic life sciences as distinct disciplines, so that the trainees are exposed to the diverse disciplines involved in ART. Alternatively, universities or other institutions having the appropriate basic science departments can offer training for the laboratory staff, and medical institutions can offer training in the clinical aspects of ART. Nevertheless, there must be a nodal point where the staff trained in the above two types of institutions can come and work together to acquire capabilities of practicing ART. Speciality ART clinics, either in the public or the private sector, can act as such nodal points and play a major role in establishing such training programmes.

Scientific discoveries and advances, especially in modern biological sciences, are occurring at a very rapid pace. There is concomitant development of new reproductive technologies. Training in ART should, therefore, be a continuous and an ongoing process. The only way in which already trained staff could keep up with the new advances is to take part in workshops and conferences organized by scientific societies. The Government of India must encourage such conferences through organizations such as the ICMR, Department of Science and Technology, Department of Biotechnology, CSIR, and the various science academies in India.

Chapter 6

Future Research Prospects

6 Future Research Prospects

Progress in any field can only occur through research. There have hardly been any publications by Indian scientists in the area of ART in peer reviewed, internationally reputed, scientific journals, except for a few that appeared from the Institute for Research in Reproduction in the late 1980's. Consequently, much of ART practice that is used in India is based on papers published outside India, and there is hardly any information either on the basic profile of the infertile couples in India or even on the clinical experience in respect of the ART technologies developed elsewhere but used in India as per the Western protocols.

ART offers a unique situation to study the biology of reproduction in human subjects without compromising ethical issues. For example, it is perfectly legitimate and ethical to take tissue and body fluid samples from an infertile couple to study the cause of infertility. This is an area that has not been exploited in India. Another line of research that is extremely important is to study early embryonic development – subject that has remained in darkness for quite a long time. What kinds of genes are turned on and off at different stages of pre-implantation embryos? This would aid in developing methods for implanting only the appropriate embryos in individuals who are known carriers of inheritable genetic disorders. Can embryos be used for developing tissues or organs (kidneys, pancreas etc.) for replacement? Stem cells obtained from developing embryos hold much promise in this field of biotechnology. There is hardly any serious research going on in such areas in the country. It must be borne in mind that one important area of future medical advances, is gene therapy, and such therapy may require *in vitro* fertilization and development.

What is urgently required is the identification of projects that are of value to advance our knowledge of human reproduction and develop better methods for treating infertility, or even identify better contraceptives because infertility is the kind of situation that we intend to create in a fertile couple desirous of limiting their family size. Following such identification, research in reproduction, with special reference to infertility treatment, must be

identified as a priority area for research for funding by the national scientific agencies.

6.1 Pre-implantation Genetic Diagnosis and Chromosomal and Single-Gene Defects

There is a growing volume of information that is now available showing that many forms of infertility are caused by genetically transmittable disorders. The genetic disorders include trisomy, translocations, inversions, deletions and microdeletions. All this new information suggests that great care must be exercised with ART because infertile couple may be carriers of such disorders; when one tries to force fertilization, the question arises whether one is transmitting genetic disorders to the offspring. This raises many moral and ethical issues.

One way to get around this problem is to institute top-class genetic diagnostic facilities that will be able to carry out diagnosis of genetic defects in single cells obtained from embryos. This is a very expensive and labor-intensive project and therefore there is a need to establish just a few well-equipped centers in the country and later expand them if there is a need. These centers could serve as referral centers and should be used judiciously. The establishment of such centers will go a long way in placing ART practice in India on a firm, healthy and ethical footing.

Chapter 7

Providing ART services to the Economically Weaker Sections of the Society

7.0 Providing ART services to the Economically Weaker Sections of the Society

7.1 The setting up of a modern ART clinic and running it satisfactorily is an expensive affair, requiring a dedicated staff that would render long-term service. The setting up of ART clinics in the public sector, which do not exist as of now, must be explored.

7.2 *Reduction of drug costs:* The concerned Ministries must take a look at the reason for the high cost of ovarian stimulation hormones, and encourage and support local pharmaceutical industries to start manufacture of human menopausal gonadotropins indigenously so that the treatment of our infertility patients is not dictated by the commercial motives of the multinational pharmaceutical companies but by national needs.

Chapter 8

Establishing a National Database for Human Infertility

8 Establishing a National Database for Human Infertility

It is important to realize that diagnostic and therapeutic approaches in reproductive medicine have to keep pace with rapidly developing molecular knowledge of human reproduction. It is now possible to detect the incidence of chromosomal abnormalities using a variety of high-powered PCR techniques (Human Reproduction 13: 3032-3038, 1998.) and multicolour fluorescent *in situ* hybridization (FISH) analysis (Chromosome 6:481-486,1998; Human Reproduction 16:115-120,2001). FISH studies on sperm are becoming necessary to understand whether there is a genetic cause for male infertility, before patients can be subjected to ICSI. New spermatogenesis genes are bound to be discovered (Endocrinological Investigations 23: 584-591, 2000); testing their mutation will become easier with DNA chips and microarray technology.

Unfortunately, there is no documented database available in our country that would cover data on all aspects of infertility, and there is an urgent need for the same. It is worrisome to see that, with the primary aim of providing a child to the infertile couple, a variety of sophisticated ART are being used to overcome male factor infertility without understanding the underlying cellular and molecular etiology. In the process of curing infertility in the patient, there is a high iatrogenic risk of transmitting an abnormal paternal geno-(pheno-)type to the ART-born child. An appropriate database would allow the quantification of such risks.

Chapter 9

Composition of the National Advisory Committee

9 Composition of the National Advisory Committee

Chairman: Secretary, Ministry of Health and Family Welfare, Govt. of India.

Co-chairman: Director General, Indian Council of Medical Research, New Delhi.

Executive Secretary: A officer below the rank of Joint Secretary in Ministry of Health and Family Welfare, Govt. of India.

Members:

- Representative of the Indian Council of Medical Research.
- Representative of the National Academy of Medical Sciences.
- Representative from the Ministry of Health & Family Welfare, Govt. of India.
- Representative of a scientific society that deals with ART. Care must be taken to ensure that such a representative should be from a society that has democratically elected office bearers and is governed by reasonable rules and regulations. The representative must have a proven track record of having contributed significantly to ART. The nature of the person's association with commercial companies must be made known publicly.
- A social scientist of repute.
- The Chairman of the National Bioethics Committee.
- A gynaecological endocrinologist.
- A gynaecological sonographist.
- An operative gynaecologist.
- A mammalian reproductive biologist.
- An andrologist.
- A representative of NGOs.

- A counsellor.
- A representative of patients.
- A medico-legal expert.
- A representative of FOGSI.
- A representative of ISSRF.

Notes: 1. A meeting of the National Advisory Committee may be chaired either by the Chairman or Co-chairman.

2. The Advisory Committee should meet at least once in six months.

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