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

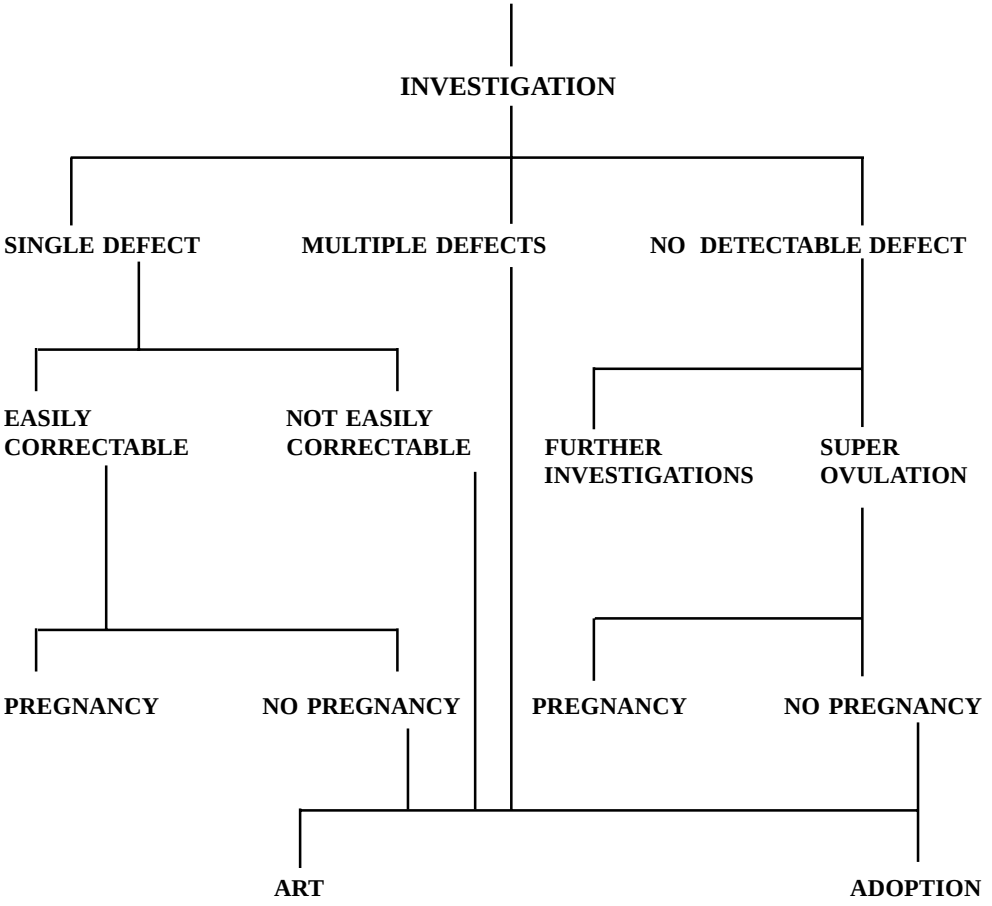
When multiple defects involve either one or both partners, attempt to correct these defects and hoping to achieve a pregnancy in the natural way is almost always unrewarding. This should be explained by the consulting gynaecologist/physician to the couple to prevent unnecessary expenditure by the couple. 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.