

Reviews

In vitro fertilization and embryo transfer

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Patient selection for in vitro fertilization (IVF) and embryo transfer (ET)

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The setting up of the in vitro fertilization (IVF), with embryo-transfer (ET) to the maternal uterus (defined by some groups as embryo-replacement, ER), as a treatment for infertility, foresees a considerable engagement of both human and economic resources. Moreover, the handling of human embryos causes obvious ethical problems. For these reasons, it is imperative that patients entering the IVF-ET program are properly selected. First, there must be adequate indications for the treatment. Secondly, patients must meet general and particular prerequisites in order to avoid risks and to maximize possibilities for success.

I. Indications for IVF-ET

The 'Committee for Bioethics in the Handling of Human Gametes and Embryos' established by the 'Swiss Academy of medical Sciences', stated, in April 1984, that 'IVF and ET are scientifically and ethically justifiable if other methods of treatment have failed or offer no prospect of success'. Other institutions have made similar statements. For example, the ad hoc Committee of the American Fertility Society stated that 'in vitro fertilization for infertility not solvable by other means is considered ethical'⁴. The main indication is irreparable bilateral tubal damage^{20,41} which was the type of infertility for which IVF-ET treatment was originally developed³⁷.

Other indications^{23,29} are represented by conditions of infertility previously treated with traditional therapy for an adequate period of time, or having passed an adequate period of time from the treatment cycle, giving scarce or no probability for resolution. When considering these indications it is important to keep in mind:

a) that – as a consequence of the fact that the probability

of pregnancy for each ovulatory cycle is low (20–25%) even for young fertile couples^{7,18} – when sub-fertility factors are present, pregnancy can be achieved after years even spontaneously^{1,9,13,31,38,39}.

b) that for patients over 35 years of age, besides the well-known biological problems for the possible conceptus, fecundity is reduced^{14,21}.

For some of these conditions other techniques recently proposed and partially derived from IVF-ET methodologies, may be considered: 1. in vitro sperm capacitation and transcervical intrauterine insemination (IUI) with concomitant controlled ovarian hyperstimulation³⁵; 2. more importantly, the translaparoscopic gamete intrafallopian transfer (GIFT)⁵. These techniques are less expensive and avoid the manipulation of embryos, thus less ethical problems arise.

Tubal infertility

a) *Fallopian tubes absent* – e.g. for agenesis or after bilateral ectopic pregnancies or surgical ablation for severe pelvic sepsis. In these cases IVF-ET obviously represents the only possibility.

b) *Previous reparative surgery*. The failure of previous surgery represents, in general – especially if the patient is over 30 years of age – an indication for IVF-ET; in fact, the chances offered by further surgery are limited³³. It is evident that a certain period of time must pass to establish the failure of the surgical treatment. This point has been recently reviewed by Schoysman³³ on the basis of the type of tubal damage and of the surgery performed. In general, IVF-ET is indicated 1–2 years after surgery. In addition, other possible factors (male, cervical, etc.) and age of the patient must be considered.

c) *Tubal microsurgery versus IVF-ET*. This problem has also been reviewed by Schoysman³³. Ovariolysis or salpingolysis performed by a skilled microsurgeon offers good possibility for success; thus, surgery is the treatment of choice particularly for women under 35. Good results are also obtained by an adhesiolysis performed during laparoscopy³⁴. On the contrary, more complex surgical procedures (ovario-salpingolysis, fimbrioplasty, salpingoplasty, tubal implantations) do not offer good possibility for success; therefore IVF-ET is definitely indicated for women over 35³³. IVF-ET should also be used when the following alterations, for which surgery is contraindicated, are present³³: damage of the tubal mucosa, thick-walled hydrosalpinx, and 'tortuous' tubes. This last alteration – of which the diagnosis may be made particularly with chromolaparoscopy – apparently seems to be minor: however, even though a spontaneous pregnancy can be obtained sporadically, other types of treatment are not successful³³.

Endometriosis

Results obtained by IVF-ET in women with endometriosis are satisfactory and comparable to those of women with tubal infertility^{23,24,29}.

Mild cases of endometriosis often permit a spontaneous pregnancy^{16,36}. Even in moderate and severe cases, a high pregnancy rate is obtained with medical and/or surgical treatment^{16,36}. Generally, pregnancy is obtained within a year of treatment^{6,36}; if pregnancy does not occur within 3 years of surgery the chances are poor that it will ever occur³⁶. The prognosis not only depends on the severity of the lesion, but also on the age and on the duration of infertility: the probability of pregnancy is poor after 35 years of age and when infertility is present for more than 5 years²⁵. If follows that IVF-ET should be indicated one or two years after the previous unsuccessful treatment, considering each case individually. In cases with a very poor prognosis (endometriosis with bilateral tubal involvement; age > 35; infertility lasting > 5 years) IVF-ET may be directly indicated following possible preparatory surgery³³. In cases of endometriosis without tubal involvement GIFT may be useful.

Unexplained infertility

Infertility of unknown etiology is a condition for which there was no rational therapy^{3,38}. In these cases IVF-ET has been applied successfully^{19,23,24,29}. Cases of unexplained infertility show, in some series^{23,39}, a slightly but significantly reduced in vitro fertilization rate, with respect to cases of tubal occlusion or endometriosis. However, pregnancy rates following embryo replacement do not appear reduced^{23,24,29}; thus, it is possible to exclude any contribution of implantation failure or hostility of uterine environment in the pathogenesis of 'unexplained' infertility²⁹. Overall, the results suggest that factors such as gametes transport – and particularly sperm transport³ – to the site of fertilization are involved²⁹.

When unexplained infertility is present for less than 5–6 years there is still a certain possibility for spontaneous pregnancy³⁸. For this reason IVF-ET is used when infertility has lasted for at least 5 years¹⁹. It is important to consider the age factor: while it is reasonable to wait at least 6 years for women under 35, for women over 35 this

waiting period should be reduced. It has been seen that the possibility of a spontaneous pregnancy increases within 1–2 years of a diagnostic laparoscopy³⁹; such a chance is possible even if infertility has lasted for more than 5 years, but it is reduced for women over 35. Laparoscopy is essential for the diagnosis of unexplained infertility; a subsequent waiting period of at least two years for women < 35 and of at least 6–12 months for women > 35 seems to be reasonable before an IVF-ET attempt. GIFT represents a valid alternative to IVF-ET in cases of unexplained infertility⁵. The technique of IUI with capacitated sperm may also be useful³⁵.

Male factor

Seminal fluid alterations significantly reduce the possibility of an in vitro fertilization^{23,24,28,29}. The most important limiting factor seems to be sperm motility^{12,28}, particularly when seminal fluid inflammation¹² or sperm autoantibodies are present²³; according to Mahadevan and Trounson²⁸ fertilization fails when initial motility is < 20% and motility after capacitation is < 30%. However, using special procedures in collecting and treating seminal fluid, it has been possible by some authors^{11,12} to obtain an in vitro fertilization even in cases with severe sperm alterations; the pregnancy rate following embryo replacement was good and the incidence of abortion was not raised in comparison with other IVF-ET patients¹². On the basis of these results, IVF-ET has been proposed as a treatment for male infertility^{11,12}. Others are in agreement with this suggestion, provided that such patients are properly counselled⁴⁵; in fact, it has been found that failure of in vitro fertilization can cause severe psychological problems.

When dyspermia is present and infertility lasts for more than 6 years, the possibility of obtaining a pregnancy is, on the whole, not greater than 10% even with appropriate traditional therapy¹; in single cases, when the alteration is severe, the probability is practically zero. Therefore, IVF-ET may be justifiable in these cases. The validity of other techniques, such as IUI³⁵ and GIFT⁵, as an alternative to IVF-ET in cases of severe dyspermia, needs clarification.

Female immunologic infertility

Infertility may be caused by the presence of antisperm antibodies in the female, generally interfering with sperm transport especially in the cervical mucus^{9,31}. The spontaneous resolution of this type of infertility is not infrequent^{9,31}. However, when infertility is present for years and/or the antibody levels are constantly high, the probability of a pregnancy, spontaneous or following traditional therapy, is very limited^{9,31}.

IVF-ET has been successful in patients with antisperm antibodies^{23,44}. Using special procedures for the manipulation of oocytes, a pregnancy in a patient with antibodies even in the follicular fluid was obtained².

II. General prerequisites of the IVF-ET patients

Laboratory tests excluding causes that may interfere either with pregnancy or with fetal or mother health^{19,41}: Hb electrophoresis for hemoglobinopathies; serum tests for

syphilis; antibodies against Rubella²⁶ and Toxoplasmosis; Hbs-Ag; vaginal cytological and bacteriological examinations with particular search for Chlamydia, Mycoplasma and Neisseria Gonorrhoeae; tests for metabolic diseases. Moreover: chest X-ray; careful breast evaluation.

Hereditary diseases should be excluded by a careful family history.

Psychological evaluation of the couple is of great importance⁴¹ either to single out problems which may contraindicate the therapeutical attempt, or to define the opportunity of a psychological support during the stressing and possibly long process the couple must face.

Data obtained by some groups^{24,29} suggest that the biological fitness for IVF-ET is substantially independent of patient age if ovulation occurs. Trounson's group admits to IVF-ET procedure women up to 45 years⁴⁰. However, Edwards and coworkers¹⁹ found that the possibility of giving birth after IVF-ET is reduced as age increases, due to a higher abortion rate. Consequently as agreed by most IVF-ET groups²⁰, women over 40 years should be excluded.

III. Particular prerequisites of IVF-ET couples

Absence of current pelvic inflammatory disease;

Spontaneous or induced ovulatory cycles with normal endocrine profiles (temperature charts; progesterone and prolactin evaluation);

Ovaries accessibility for laparoscopic oocyte collection, documented by preliminary laparoscopy^{19,41}. Even though ultrasonical guided percutaneous aspiration of oocytes has been proposed^{27,42,43} and currently adopted by some

workers²², most groups^{17,19,24} still prefer pick-up of oocytes by laparoscopy. In some cases, accessibility may be obtained by adhesiolysis under laparoscopy or, if the case, by laparotomy, with possible transposition of ovary in an accessible seat^{15,41}. Preliminary laparoscopy may define the accessibility of only one ovary; in such a case oocyte collection must be restricted to cycles when mature follicles are developing in that ovary, as determined by ultrasound evaluation⁴¹. Some authors¹⁷ think preliminary laparoscopy is not necessary when diagnosis of severe tubal damage is already certain; in their opinion, when necessary, the ovaries may be cleared of obstructing adhesions during the laparoscopy scheduled for oocyte retrieval¹⁷. Ultrasonical guided oocytes collection is the only alternative in the case that neither ovary is accessible because of remarkable adhesions.

*A normal uterus as evaluated by hysterosalpingography or hysteroscopy*⁸ is essential. The exam must be repeated if potential causes of uterine alteration (diagnostic or therapeutic curettage, etc.) subsequently occurred.

Finally, it is important that the male partner produces a *satisfactory seminal fluid*. As stated above (see Indications for IVF-ET. Male factor), IVF-ET has given positive results in cases of semen deficiency^{11,12,19,20,23,24,29,45}; however, it is important to remember that seminal alterations, particularly motility alterations, significantly reduce the fertilization rate^{28,29}. Therefore, it is our opinion that IVF-ET should be limited in these cases, at least at the beginning of a group's clinical procedure. Seminal fluid must be analyzed at least twice by a reliable laboratory. If the semen is normal⁶ the couple is admitted to IVF-ET procedure. If the semen test is unsatisfactory, an andrological control and a further semen test with bacteriological sperm culture³⁰ are requested. After adequate treatment further controls are required.

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Genetic screening of in vitro fertilization (IVF)–embryo transfer (ET) patients

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Key words. In vitro fertilization; embryo transfer; genetic screening; X-chromosomal recessive disease.

Although it is not customary that a couple undergoing investigation and therapy for sterility is also screened for genetic defects, such an approach might be envisaged in IVF–ET for several reasons:

- 1) The procedure is time-consuming and expensive not only for the couple concerned but also for society and for the scientific community. Much research is still being done to improve the techniques and a lot of money has been spent already since the first experiments were started². Therefore, it could be argued that there are more important issues to spend money for than IVF–ET. But the wheels cannot be turned back, and we have to face the facts and try to make the best of it. This means that, when IVF–ET becomes a routine treatment for sterility, risks should be kept as low as possible. This can be accomplished to a certain extent by genetic screening and selection of candidates.
- 2) Another argument in favor of a genetic evaluation of patients for IVF–ET is the psychological burden of this

procedure for the prospective parents as well as for the physicians involved. This implies that there must be the greatest possible reduction of risk to the fetus, and this, again, can be accomplished by a genetic screening of the couple, among other measures.

Selection of patients for IVF–ET should consider the following genetical aspects:

- 1) Seriously debilitating multifactorial traits should not be present in the couple or in more than one close relative. Among common multifactorial traits some present serious handicaps, whereas others are of little medical importance. In some cases it is open to debate how serious the ensuing handicap is in personal and social terms. In these, the wish of a couple to conceive a child (even by means of IVF–ET) may be greater than their fear of the respective disease. Cleft lip and palate, pyloric stenosis, club foot and diabetes are examples of this type