



european society of human reproduction & embryology

## **Good Clinical Treatment in Assisted Reproduction - An ESHRE position paper**

### **EXECUTIVE SUMMARY**

**June 2008**

The prevalence of infertility is increasing in the developed world. The postponement of pregnancy, greater prevalence of obesity and sexually transmitted infections all contribute to the problem. This trend has been acknowledged by the European Parliament, which in February 2008 called on Member States "to ensure the right of couples to universal access to infertility treatment". As a result, there exists a progressive need for medical help in resolving reproductive disorders.

ESHRE, as the European body for professionals in reproductive medicine and biology, has through its membership always aimed to provide childless couples with the best possible management of their fertility problems, while at the same time ensuring that they are not exposed to unnecessary risks or ineffective treatments. It is ESHRE's view that the treatment of infertility should be based on a balanced choice from the best available evidence, with respect both to efficacy and safety. ESHRE promotes improvements in medical and laboratory practice and encourages, through its educational activities and training, high quality medical care and laboratory procedures. It is the objective of ESHRE to describe in this position paper the principles of good clinical treatment in assisted reproduction from an evidence-based professional perspective.

Accessibility is a key feature of good clinical care. Treatments of proven benefit should be made easily available throughout Europe, irrespective of the patient's income or place of residence. Reimbursement policies have an impact on the use of reproductive health care; a lack of reimbursement constitutes a barrier for those seeking treatment. Individual EU countries should provide access to publicly funded health care, inclusive of, but not limited to, assisted reproductive technologies such as intrauterine insemination (IUI), in vitro fertilisation (IVF), and intracytoplasmic sperm injection (ICSI).

It has been shown that 84% of couples not using contraception and having regular sexual intercourse will conceive within one year; another 8% will conceive in their second year of trying. So, the first objective of a dedicated fertility investigation should be to identify those couples who most likely will not need medical assistance. As involuntary childlessness can be a psychological burden, proper counselling should be offered about all related medical, psychological and social questions. Providing them with easily understood evidence-based information should offer couples the opportunity to make informed decisions with regard to their reproductive future and the care they wish to receive.

In couples in whom screening reveals a problem, further delay is not justified and treatment should be offered. This may include advice on lifestyle changes, eating habits, smoking and stressful employment. It may also include medical treatment with drugs, the induction of ovulation, surgery, insemination, IVF, ICSI, and oocyte or sperm donation (sometimes after cryopreservation).

Modern techniques of assisted reproduction have been accompanied by high risks in the past: ovarian hyperstimulation syndrome, thromboembolism, (high order) multiple pregnancies, surgical complications. Within ESHRE, responsibility for high quality patient care has stimulated the development of mild approaches in IVF, the encouragement of elective single embryo transfer, the development of improved freezing programmes, and the abandonment of aggressive surgical procedures in favour of minimally invasive surgery.

In order to ensure proper monitoring of both quality and quantity in assisted reproduction, it is important that annual reports according to the principles outlined by ESHRE with respect to types, efficacy, safety and risks are made publicly available.

Dedicated, responsible care for childless couples together with universal access to infertility treatment should be a common goal of ESHRE, patient organisations and EU politicians alike.

## **INTRODUCTION**

Despite international calls for preventative measures and ready access to appropriate treatment, infertility is still a major problem in the developed world (United Nations 1994). The increased prevalence of infertility in recent years can at least be partly attributed to such lifestyle factors as obesity and smoking and to the high incidence of sexually transmitted infections such as Chlamydia. In addition, postponement of a first pregnancy is increasingly common in the developed world (Commission of the European Communities 2005, Commission of the European Communities 2006); this too can lead to ovarian ageing and associated infertility.

The difficulty some face in accessing appropriate advice and treatment has also been recently acknowledged by the European Parliament which, in a resolution adopted on 21 February 2008, said that it "calls on the Member States, therefore, to ensure the right of couples to universal access to infertility treatment" (European Parliament 2008).

Taken together, they imply and reflect a progressive increase in the need for assisted reproductive technology (ART) treatment (ESHRE EIM data).

As the European body for professionals in reproductive medicine and biology, ESHRE aims to ensure that patients throughout Europe receive the best possible treatment and are not exposed to unnecessary risks. This means that treatments offered should be based on the best available evidence with respect to efficacy and safety. The role of ESHRE is also to support improvements in the field of medical practice and to promote the safety and quality of clinical, surgical and laboratory procedures.

ESHRE considers it a fundamental principle that professionals in reproductive medicine and biology are allowed to utilise the full biological potential of gametes and embryos. Against this background, ESHRE finds it important that there is coherence between a country's decision to support assisted reproduction and the financial and regulatory strategies affecting the quality of the service provided.

The objective of this paper is to describe the principles of good clinical treatment within selected areas of assisted reproduction from an evidence-based professional perspective. Very important areas of fertility treatment including surgery, problems during implantation and early pregnancy are intentionally omitted from this document.

## **ACCESSIBILITY**

A fundamental basis for providing assisted reproduction is that the different treatments are easily available. Further, current evidence shows that reimbursement policies can have significant impact on the accessibility and use of ART treatments, and that lack of medical reimbursement will act as a barrier to the use of ART.

In order to provide good fertility treatment individual countries should provide access to publicly funded ART in a realistic, timely and dedicated manner. All countries should be in a position to document that they provide a public programme on a scale which is consistent with the real need for ART and without a waiting-time that has a negative impact on success rates.

## **INVESTIGATION OF FERTILITY PROBLEMS**

People who are concerned about their fertility should be informed that some 84% of couples in the general population will conceive within one year if they do not use contraception and have regular sexual intercourse. Additionally, they should be informed that female fertility declines with age. Women and men should also be informed about the possible negative effects of alcohol, smoking and body weight (overweight and underweight) on fertility, and preconceptional care should focus on assessing the risks of treatment and pregnancy in each individual case. Couples who have not conceived after one year of regular unprotected sexual intercourse should be offered further clinical investigation, including semen analysis and assessment of ovulation.

An appropriate hormonal investigation should be offered when there are signs of ovulation disorders. Semen analysis should be performed based on the recommendations of WHO and ESHRE. Further tests, including clinical andrological investigation, are advised in cases where abnormalities are detected.

The results of semen analysis and ovulation assessment should be known before a test of tubal patency is performed. Women thought to have co-morbidities should be offered laparoscopy, so that any tubal and other pelvic pathology can be investigated and treated at the same time. The ovaries can be assessed by vaginal ultrasound. In some cases hysteroscopy may be indicated.

Based on the outcome of the investigation, each couple should receive information which includes an estimate of their chance of spontaneous pregnancy and their chance of pregnancy after different treatment options. This information should be provided in a form that it is accessible to people with additional needs, such as those with physical, cognitive and sensory disabilities, and those who do not speak the native language.

### **INFORMATION AND COUNSELLING**

Patients should have the opportunity to make informed decisions about their care and treatment based on evidence-based information. These decisions should be recognised as an integral part of the decision-making process. Verbal information should be supplemented by written and/or audio-visual material, including information about other options such as adoption. Contacts to fertility support groups should be identified.

As involuntary childlessness can be a psychological burden, counselling should be offered which raises all related medical, psychological and social questions. Counselling should be an integral part of each centre's programme and should be performed by physicians, nurses and/or professional counsellors.

Counselling should be offered before, during and after investigation and treatment, irrespective of the outcome of these procedures, and patients should be informed that stress in the male and/or female partner can affect relationships and have a negative influence on sexuality.

### **OVULATION INDUCTION**

Ovulation induction aims to restore fertility in anovulatory women. It should be offered taking into account other factors, such as male or pelvic factors, weight or eating disorders, stress or over-exercise. Thus, at least one semen analysis from the male partner should be performed before ovulation induction is offered, and tubal patency checked as appropriate according to clinical history.

If there are no concerns about pelvic or tubal health, it may be appropriate to perform three cycles of ovulation induction prior to checking tubal patency.

When an ovulation disorder is present, treatment is offered according to aetiology:

1. Women with a low or high BMI should first be offered counselling with respect to eating habits or stress. This is also important for those suffering from polycystic ovary syndrome, who may resume ovulation with weight loss.
2. Clomiphene citrate remains the first-line medical treatment and can be given for up to 12 months. Patients should be informed of the small risk of multiple pregnancy. Anovulatory women with polycystic ovary syndrome and BMI >25, who have not responded to clomiphene alone, may be offered metformin in addition.
3. Gonadotrophin therapy is appropriate for women who fail to ovulate or conceive with anti-estrogen therapy (clomiphene citrate), or have hypothalamic failure or dysfunction. For the latter group, pulsatile LHRH treatment is also appropriate and generally presents a lower risk of multiple pregnancy. Nevertheless, any centre carrying out ovulation induction with gonadotrophins should have facilities for regular monitoring with ultrasound, and expertise in monitoring such cycles.

4. Women with hyperprolactinaemia should be offered treatment with dopamine agonists such as bromocriptine or cabergoline after checking for thyroid function and correcting any anomalies.

#### **INTRAUTERINE INSEMINATION (IUI)**

Although IUI represents a “mild” ART procedure, it must be performed with care, according to strict criteria. Tubal patency as well as semen quality must be checked prior to performing IUI.

There is general agreement in the literature that chances of success are better after mild ovarian stimulation and the maturation of a maximum of two or three follicles. However, the cycle must be monitored by ultrasound and hormonal analysis; if there are more than three mature follicles, the attempt should be cancelled. While the concurrent use of ovarian stimulation may increase pregnancy rates, it may be at the expense of a high chance of multiple pregnancy.

The majority of pregnancies occur during the first six cycles. In any case, the number of attempts should not exceed nine cycles. When assessing the duration of an IUI programme, the age of the woman must be taken into account, to ensure timely transfer to more complex treatments if indicated.

#### **IN VITRO FERTILISATION (IVF)**

Bilateral lack of tubal permeability represents an absolute indication for performing IVF. Other indications include doubtful tubal patency, endometriosis, moderate alterations of semen characteristics, unexplained infertility or failure of several previous cycles of ovulation induction or IUI. IVF must be offered as a first-line treatment in women of advanced maternal age, irrespective of the cause of infertility. Conventional IVF should not be proposed in the presence of severe sperm abnormalities, or after several fertilisation failures in previous attempts.

#### **INTRACYTOPLASMIC SPERM INJECTIONS (ICSI)**

ICSI should be considered in the presence of severe sperm abnormalities or a history of fertilisation failure in conventional IVF attempts. It must be emphasised that ICSI does not represent the most suitable treatment for female pathologies such as poor ovarian response or previous implantation failures.

#### **CRYOPRESERVATION**

Given that excess embryos are usually obtained during IVF/ICSI treatments, the cryopreservation of embryos should be routinely available as an integral part of infertility services. The establishment of a successful cryopreservation programme will increase cumulative live birth rates and also make single embryo transfer an increasingly efficient option. With a higher number of elective single embryo transfer cycles, more good quality embryos are available for cryopreservation. Cryopreservation not only makes these embryos available for future use by the couple, but may also be useful in avoiding the risks of ovarian hyperstimulation.

#### **MULTIPLE PREGNANCIES**

The most common complication of ART is multiple pregnancy. Maternal morbidity and mortality in multiple pregnancies are significantly increased when compared to singleton pregnancies. Twins are associated with higher rates of perinatal complications. The risk of neurological problems in newborns, cerebral palsy included, is higher than in singletons. Twin pregnancies are increasingly accepted as a serious complication of ART for the couple, the newborn and society.

The decline in the number of multiple births can be regulated only with a reduction of the number of embryos transferred. This restrictive embryo transfer policy could be accepted as the only means of eliminating high order multiple gestations. Although the transfer of two embryos has prevented triplet pregnancy, twin pregnancies still account for more than ~25% of deliveries after two early stage embryos are transferred or more than ~35% when two blastocysts are transferred.

## **SINGLE EMBRYO TRANSFER POLICY**

Single embryo transfer (SET) in selected groups of patients is advocated as the only effective means of lowering the rate of twin pregnancies. The transfer of one good quality embryo from at least two available can reduce the twin pregnancy rate significantly. The implementation of elective SET is possible only in combination with high quality laboratories and good cryopreservation programmes.

Guidelines for which patients are eligible for elective SET should include the woman's age, number of previous IVF/ICSI cycles and embryo quality.

Recent observational studies are indicative of relatively poor outcomes in cases where only one embryo was available, and of good results when an elective single embryo was selected for transfer.

A systematic Cochrane review of randomised studies demonstrates a decrease in the chance of live birth in fresh IVF/ICSI cycles after elective SET in comparison with double embryo transfer (DET). However, the combination of SET with a good quality freezing programme and subsequent replacement of a single frozen-thawed embryo achieves a live birth rate comparable with DET.

Transfer of three and four embryos should be discouraged.

A two embryo transfer policy is now common in most European countries. Elective SET is today part of the embryo transfer policy (by legislation and/or guidelines/voluntary agreement) in five EU countries.

## **MONITORING**

In order to ensure the full monitoring of both quality and quantity in ART it is important that annual reports, compiled according to the principle outlined by ESHRE covering types, efficacy, safety and risks, are made publicly available. Data monitoring of ART should be performed both at the level of individual clinics and as an independent, authority-based national registry.

References:

The document is based on ESHRE and NICE guidelines, ESHRE monographs and EIM reports.