

## INTERNATIONAL CORNER

## THE STATE OF ASSISTED REPRODUCTION TECHNIQUES (A.R.T.)

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## INTRODUCTION

I have always believed that the social controversy generated by Assisted Reproduction Technologies (A.R.T.) was due to the fact that these techniques affect health and change something very classic: the way in which we humans have to reproduce ourselves. Everything that we doctors and biologists working in this discipline can do to transmit the maximum amount of information to society will help to avoid what Testart defined as "show-business procreation".

In the western world there is an obvious fall in human fertility, and in Barcelona we reached zero growth several times in the late nineties. This decrease can be explained both by the voluntary infertility of many couples who follow certain contraceptive methods with the aim of avoiding a pregnancy and by the loss of reproductive potential caused by the postponement of motherhood until more advanced ages when the woman is already physiologically less fertile.

## EPIDEMIOLOGY

The human species has the poorest reproductive potential of any in the animal kingdom. There are numerous epidemiological studies that show that the possibility of a supposedly fertile couple in which the woman is less than 30 years old achieving a pregnancy in one month does not exceed 25% (1). According to WHO data from the end of the last century, it was estimated that there were 60-80 million infertile couples in the world who could not have the child that they wanted. In Spain the National Statistical Institute accepts that 15% of couples of child-bearing age have problems with reproduction and it is admitted that every year there are 44,000 new sub-fertile couples. It must be borne in mind that the majority of these couples still have a certain expectation of achieving a pregnancy spontaneously, though these possibilities will fall as the woman's age increases. It is obvious that modern society, with the great professional pressure that young women are subject to, is responsible for the delay with which many women take the decision to have their first child. Nor should it be forgotten that natural monthly fertility falls to 8% at 35 years and to 3% at 38.

There is a social aspect that cannot be ignored. The birth rate in my country has fallen by 50% in the last 30 years, the mean number of children per couple of child-bearing age is 1.1, and the percentage of women who have their first child when they are more than 35 years old has increased by 30% in the last 10 years. This phenomenon is further evidence of the imbalance that exists between the poor and overpopulated South and the North, which is rich but has no generational replacement and where situ-

ations arise such as that known by the acronym DINK (dual income no kids) where the couples decide voluntarily not to have children and to enjoy the financial well-being provided by the two incomes.

In these days of ecological impregnation in which we live, I wonder whether it is necessary to medicalise reproduction; sometimes medical interference may seem offensive in such personal aspects as the reproductive process of our species. Our responsibility is no more than helping those couples who wish to have children to do so while providing appropriate contraceptive methods to couples who decide temporarily not to have them. The gynaecologist has to accompany the woman through her biological evolution, helping her to solve her problems out of respect for the personal situation of each couple and not from a wider demographic policy.

All the analyses will be valid in explaining the apparent reproductive poverty of this baby-boom generation, which was expected to contribute to overcoming the fall in the birth rate. Once the diagnosis has been made, that will be the time for the sociologists, the politicians and especially the doctors to join forces so that young couples can quickly have the child that they probably all desire.

## EFFICACY

The results that are currently achieved by the application of ART are increasingly high and easily exceed the monthly rates for spontaneous pregnancy of couples who come to our hospitals.

I would like to review the success rates obtained with the different techniques that we commonly use in reproductive medicine.

## INTRAUTERINE INSEMINATION (IUI)

The combination of over-stimulation of follicular growth, usually with gonadotropins, and the intrauterine insemination of a suspension of spermatozooids prepared in the laboratory is useful in treating cases of male infertility, cervical factor unexplained infertility, with very promising pregnancy rates being achieved, especially in the first 3 treatment cycles.

During the period 1995-2002 our service carried out 8166 intrauterine artificial insemination cycles with spermatozooids from the husband, and 1058 pregnancies were achieved (13% preg/cycle). As can be seen in Table I the majority of the cycles were performed under stimulation with gonadotropins and the pregnancy rates are better as the patient is younger, since below 38 years the pregnancy rate was 13.9% per treatment cycle, whereas above this age it fell to 8.7% (2-3).

A special indication for which we have also made use of this technique in recent years is the treatment of couples who are serodiscor-

dant for the human immunodeficiency virus (HIV). We included in this protocol 225 couples, who underwent 529 artificial insemination cycles with 85 pregnancies being obtained, which represents a pregnancy rate of 20% per cycle and of 37.85 per serodiscordant couple treated.

#### ARTIFICIAL INSEMINATION BY DONOR (AID)

Although the sperm microinjection or ICSI techniques help to resolve a high percentage of cases of severe male factor, there are still indications for practising artificial insemination with semen from an anonymous donor. We must not overlook the fact that the majority of secretory azoospermia as the seminal pathology of genetic origin remain dependent on this kind of insemination.

In the same period 1995-2002 we practised 2304 artificial insemination from donor cycles and we achieved 442 pregnancies, which represents a pregnancy rate per cycle of 19.2%. Once again, the woman's age had a negative influence on the results achieved, and it must be pointed out that in these cases, in which the female factor is usually normal, it is possible to do without the ovarian stimulation treatment and follow a natural cycle with good expectations for success.

In recent years there has been an important change in our society and it is increasingly common for women with no partner to ask to be treated with donor insemination. This situation is permitted under Spanish law and currently represents 30% of the AID cycles that we perform each year.

The overall results obtained between 1991 and 2003 with intrauterine insemination with the husband's semen (IUI), artificial insemination by donor (AID) and ovulation induction and timed intercourse, show that of the total of 21150 cycles performed we reached mean percentages of pregnancy of 20% per AID cycle, 20% per ovulation induction cycle and 15% per IUI cycle (Table II).

#### IN VITRO FERTILIZATION (IVF)

At the present time in vitro fertilization (IVF) techniques have proved themselves easily able to exceed the natural reproductive yield of our species. Percentages for pregnancy per IVF cycle of 40% are common in many programmes, which means that now the efficacy of IVF is more than verified.

Our IVF programme during 2003 performed 1200 follicular aspirations for oocyte recovery, obtaining pregnancy rates which, depending on the age of the patient, varied between 54% for the patients aged less than 30 and 14% for those over 40 (Table III).

There are a number of additional details that contribute to improving the yield of an IVF cycle. Something as simple as embryo transfer performed under ultrasound control makes possible a significant increase in the percentages of success for this technique (4-6) and means that it is currently used routinely in all transfers performed in our hospital. Moreover, the new technological developments that have come about recently in the IVF laboratories have made a notable contribution to the results that have been achieved (7, 8).

#### Embryo Freezing

At present embryos are frozen in practically half of the IVF cycles. Classically it used to be said that the yield from frozen human embryos was very poor. We disagree with this statement as, although it is true that the implantation rates in the fresh cycle are higher and commonly reach 25%, we believe that with a good embryo freezing and thawing programme results should be obtained that are more than acceptable. In

Table I

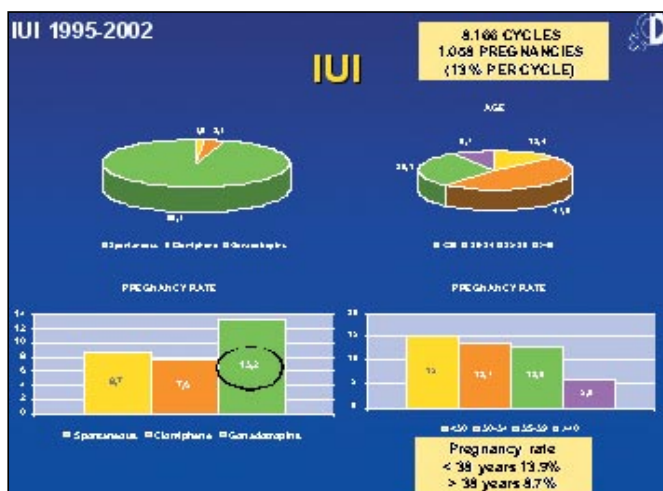


Table II

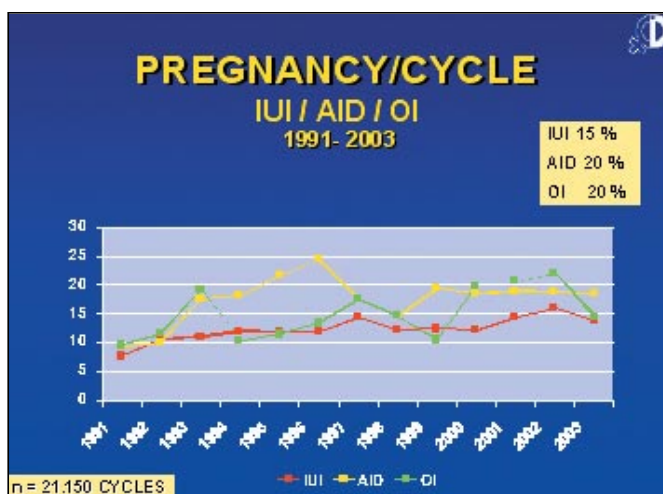
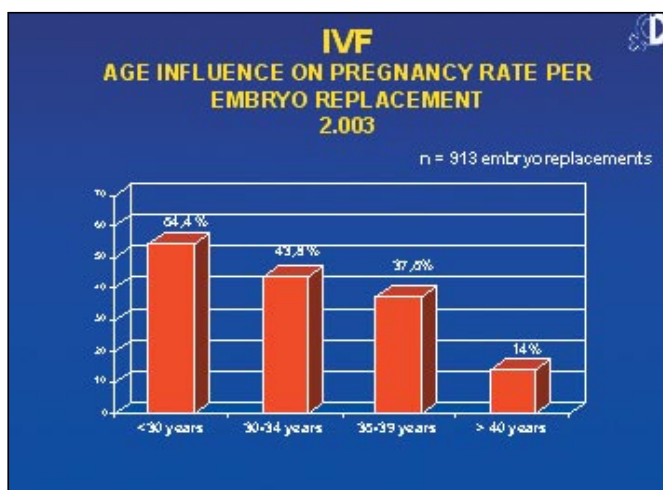
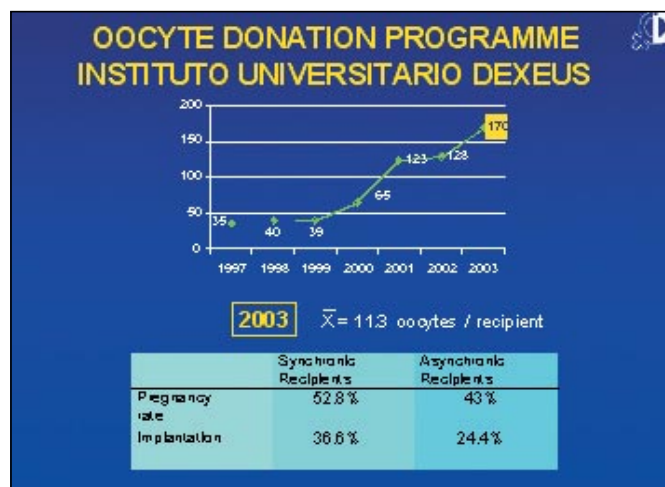


Table III



2001 we performed 368 cryotransfer cycles achieving a clinical evolving pregnancy in 116 of the cases (31.5% pregnancy per cryotransfer). It is obvious that the cryotransfer cycles that are secondary to a synchronic oocyte donation achieve higher pregnancy rates, but the attainment of

Table V



In these cases it is possible to biopsy the early embryo and extract 1-2 blastomeres which will be analysed by fluorescent in situ hybridisation (FISH) or polymerase chain reaction (PCR). With these techniques it is usual to obtain pregnancy rates of around 40% pregnancy per transfer (9-11).

Since a decade ago, when the first pregnancies were achieved following anonymous oocyte donation, the demand for this therapeutic alternative has increased considerably. It is obvious that the progressive increase in the mean age of patients who need to undergo ART brings with it an increasing number of cases that have to be treated with this technique. Although there is a worrying disproportion between the ever-increasing number of potential recipients and that of potential donors, we are fortunate in being able to reach very high pregnancy rates which, in synchronous cycles without embryo freezing, usually exceed 50%.

Apart from the high degree of efficacy of this technique there are other aspects that have to be taken into account. There is no doubt that there are very personal components that have to be gone into in depth by the couple, as in insemination with donor's semen, before resorting to the use of gametes from outside the couple. Moreover, a matter as important as the age of the recipient cannot be overlooked and although the scientific evidence is showing that pregnancy rates in oocyte donation do not worsen with the progression of age, we believe that each team must set its own age limit for accepting patients in the donation programme so as not to exceed the natural biologic limits of the onset of menopause (Table V).

There are patients who will need to resort to an anonymous embryo donation to achieve the pregnancy that they desire. In this regard Spanish legislation allows these couples to benefit from this technique. In these cases, known as prenatal adoption similar pregnancy rates are expected to those obtained in cryotransfer programmes of previously frozen embryos. That is to say, approximately one transfer in three of this kind should result in a pregnancy.

The cases of patients who have to undergo a preimplantational diagnosis are becoming more frequent. The most common reasons for needing this technique are usually:

- Sex-linked genetic anomalies
- Monogenic diseases
- Chromosomal translocations
- Advanced age of the patients
- Repeated miscarriages of unknown cause

It is beyond doubt that thanks to the high degree of efficacy of ART numerous cases of infertility have been resolved, but it must not be forgotten that these techniques are not without possible complications that must be borne in mind.

The most common complications are:

- Multiple pregnancy
- Ovarian hyperstimulation
- Gynaecological cancer

Since the early 80s there has been a considerable worldwide increase in multiple births. In Catalonia in the period 1980-1997 twin births rose from 7 to 13 per 1000 births, whereas triplets experienced an even more spectacular rise from 6 to 82 per 100000 births. This increase is connected with the systematic use of ovulation stimulation protocols, IVF and IUI or AID.

In the field of IUI, AID, or simply in ovulation induction we have been able to identify the risk factors associated with the establishment of a multiple pregnancy. We know that the risk will be significantly higher if the patient is more than 32 years old and the ovarian response to stimulation is high with levels of plasmatic oestradiol greater than 860 pg/ml and with more than 4 follicles larger than 10 mm (12, 13).

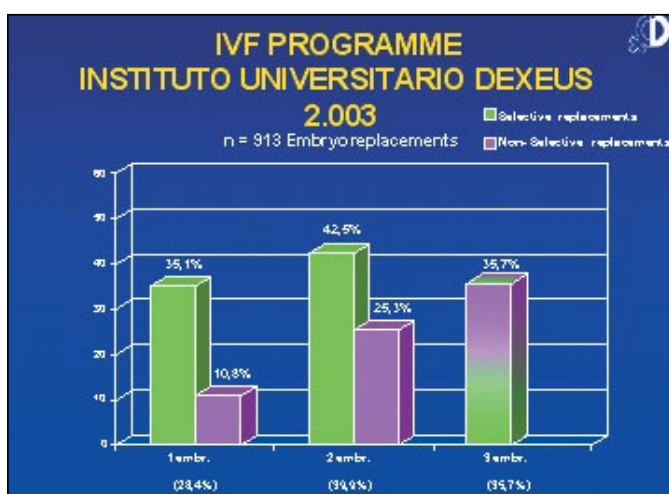
With regard to IVF, the situation is different and is also not easy to control. Usually 3 embryos have been transferred with a view to achieving adequate pregnancy rates. Currently, with implantation rates that often reach 25% we have to come up with strategies that will help to reduce the high percentages of twin or triple pregnancies in IVF. Our challenge is to avoid compromising the final clinically evolved pregnancy rate but at the same time to control the number of multiples. To this end we have designed a "Multiple Pregnancy Score" or MPS which allows us to identify the cases at high risk of multiple pregnancy in order to reduce in them the number of embryos to be transferred. After the multivariable



analysis and the application of ROC curves to our data, we found that the age of the patient and the total number of available optimal embryos are the most useful parameters in advising the transfer of 1 embryo in the cases of patients under 30 making their first attempt at IVF, in patients aged between 30-35 we can accept the transfer of 2 embryos, and this number will be 3 when the age is between 35-40 and the overall embryo quality is not excellent. However, the transfer of 4 embryos must be exceptional and only for patients aged over 40 with medium or low embryo quality.

We have recently begun to apply the selective transfer of a single embryo in patients under 35 who are in their first IVF cycle and who have good embryo quality. A comparison in these patients of the selective transfer of 1 or 2 embryos has shown that the pregnancy rates are similar, 60% and 63% pregnancy per transfer respectively, whereas the rates of twin pregnancy are practically zero for the transfer of a single embryo and very high in the group of patients who selectively received 2 embryos (14-15) (Table VI).

Table VI



#### OVARIAN HYPERSTIMULATION

Although the majority of treatment cycles usually present a certain degree of ovarian hyperstimulation, here we refer only to its severe form or genuine ovarian hyperstimulation syndrome (OHS), which is found in 1-2% of cases. This condition arises at 6-9 days from the administration of the HCG and if a pregnancy has been produced, a second outbreak originates that is secondary to embryonic HCG production.

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The serious cases are characterised by a serious haemostatic imbalance that is usually accompanied by: peripheral arterial vasodilatation, arterial hypotension, haemoconcentration, tachycardia, increase in activity of the renin-angiotensin system, ascites and hydrothorax, oliguria and sodium retention, serious liver failure.

In outline terms we can say that suitable treatment must be swift and must include: rest and compulsory hospitalisation in serious forms, low-sodium diet, plasma expanders (albumins), diuretics.

#### GYNAECOLOGICAL CANCER

ART, with their usual ovulation stimulation protocols, have been invoked as possible risk factors for gynaecological cancer. It is well known that involuntarily infertile women who have not had children have a greater risk of suffering ovarian, endometrial or breast cancer. However, in the mid-nineties some articles appeared which were based on meta-analyses of various trials and came to the conclusion that the use of ovulation inducing drugs significantly increased the risk of suffering a gynaecological cancer.

Fortunately a number of epidemiological studies appeared shortly afterwards which cast doubt on the initial hypotheses, confirming the absence of a cause-effect relationship between the use of stimulation protocols and the later appearance of a gynaecological cancer.

Although the existing scientific evidence is reassuring, a certain degree of caution must be maintained in setting up follow-up records of these patients who, probably not because of the use of ovulation-inducing drugs but from the mere fact of being infertile, have a greater risk of suffering a gynaecological cancer and must be followed up with greater rigour (16).

#### CONCLUSIONS

As we have seen, the Assisted Reproduction Techniques have achieved very high levels of efficacy and of safety, having reached an outstanding position among the therapeutic options that are available to us in reproductive medicine. However, it is obvious that their development has meant a great social convulsion and a notable change in the classic concepts of motherhood and family.

It is very true, as Einstein said, that our age is characterised by the perfection of means and by the confusion of ends. I have no doubts about the need to fight for our future, and the worst of all futures would be that in which useful science could not be developed for fear of potential abuses. I believe that information that is technically consistent and well-explained to society will be of key importance in scientific progress without loss of respect and consideration for the individual and for society.

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