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The introduction of in vitro fertilization (IVF) at the beginning of the 1980s made possible the treatment of female factor infertility. At that time the main technique used for male problems was artificial insemination by donor (AID), though in France this has always met with considerable resistance both from men and from women. Élise de LA ROCHEBROCHARD *shows that a turning point occurred in the 1990s with the emergence and rapid extension of ICSI (intracytoplasmic sperm injection), a new technique for the treatment of male factor infertility. ICSI has led to a decline in the use of AID and has stabilized the use of "conventional" IVF. With ICSI, however, male infertility continues to be treated in the bodies of women. The rapid development of this new technique, not all of whose consequences have yet been fully evaluated, raises important issues which are addressed in this article.*

With the wide diffusion of medicalized contraception (Leridon et al., 1987; Leridon et al., 2002), women could have the impression that they are living out the famous feminist slogan of the 1970s "A child if I want, when I want". Yet once the decision to have a child has been taken and contraception has been stopped, the couple's control over events ceases and a child may not happen. Of 100 young couples who embark on this adventure, a pregnancy leading to a live birth is started by 20-25 in the first month, while 65-70 conceive during the first six months and 80-85 during the first year (Spira, 1986; de Mouzon et al., 1988; Leridon, 1992). At the end of

* Translator's note: Demographers distinguish reproductive capacity from reproductive performance, and in demographic writing the term "infecundity" corresponds to involuntary infertility. English-language epidemiologists do not usually make this distinction, and for this reason the present article, though published in a journal of demography, retains the terms "male factor infertility" and "female factor infertility". They denote what demographers refer to as "infecundity".

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this year of waiting, it would seem legitimate for the 15-20 couples who have not conceived to consult a doctor to discuss this involuntary infertility.

In reality, couples can begin to worry well before a year is up. The "Family Situations and Employment" survey conducted by INED and INSEE enables us to measure this worry with two indicators(1). First, women were asked about the existence of *perceived difficulties* through the question: "Has it ever taken you longer than you wanted to get pregnant before finally succeeding?". Among the women who mentioned such difficulties in becoming pregnant, 30% reported having conceived before the end of the first year of trying (while 19% had conceived at the end of one year and 51% after more than one year). The second indicator deals with the *time before consultation*, a question that was put to women but also to men. Among those who have seen a doctor about infertility (women or/and their partner), 41% did so when they and their partner had been trying to conceive for less than a year (while 31% reported having consulted by the end of one year and 28% after this first anniversary)(2). These two indicators support the hypothesis of a growing "impatience" in couples, a hypothesis derived from a comparative analysis of fertility surveys between 1978 and 1988 published under the title "Sterility and subfecundity: from silence to impatience?" (Leridon, 1992).

A few decades ago, infertility would probably have been categorized among "women's problems"(3). Today, couples also have to consider the possibility that their problems could be of male origin. This issue of the origin of infecundity was explored in a survey of couples going to the doctor about infertility between July 1988 and June 1999 in the French départements of Indre-et-Loire, Loire-Atlantique and Haute-Vienne (Thonneau et al., 1991). Medical tests conducted on these couples revealed a sperm abnormality in three out of five cases (Table 1). These were mainly anomalies in the so-called conventional characteristics of sperm (number, motility, morphology). Nevertheless, other criteria for evaluating sperm quality have been proposed and it has been suggested that a proportion of idiopathic (i.e. unexplained) infertility could well be due to the male partner, with the man exhibiting a sperm abnormality not measured by the conventional criteria (Irvine, 1998)(4).

(1) Unpublished data. This survey was carried out in 1994 on a representative sample of men ($n=1,966$) and women ($n=3,007$) aged from 18 to 49.

(2) More women than men reported having consulted a doctor before the end of the first year (44% of women against 37% of men, $p=0.3\%$).

(3) The anthropologist Françoise Héritier-Augé observes that the woman is considered responsible for sterility in nearly every human society (Héritier-Augé, 1985, p. 12).

(4) D. Stewart Irvine (1998) discusses the difficulties of diagnosing male factor infertility. Generally, male factor infertility is diagnosed from the so-called conventional characteristics of sperm (number, motility, morphology) which are compared with recognized criteria of normality (Crosignani et al., 1994; van den Eede, 1995). However, this procedure has limits: (i) variability in spermatic characteristics exists between sperm samples from the same man; (ii) evaluation of spermatic characteristics suffers a degree of subjectivity which is reflected in a variability of results between analysis laboratories; (iii) criteria for normal sperm have been published by WHO but their pertinence for diagnosing male factor infertility is contested.

TABLE 1.– ORIGIN OF INFERTILITY IN COUPLES

Origin of infertility	Distribution		
Male related factors only	20%	58% male infertility of which:	9% azoospermia
Combination of male/female factors	38%		49% oligo – terato – asthenospermia
Female related factors only	34%		
Idiopathic (unexplained)	8%		

Source: Survey carried out on 1,686 couples who consulted a doctor for infertility between July 1988 and June 1989 in Indre-et-Loire, Loire-Atlantique and Haute-Vienne, France (Thonneau et al., 1991).

Whatever the case, in the area of infertility, the medical search for a "guilty party" seems inadequate: in two cases out of five, medical examination reveals a cause with both female and male origins (Table 1). This result has led the authors of the French survey to conclude that infertility is first and foremost a "couple's problem".

The proportion of male factor infertility could increase in the years to come. Research in developed countries has revealed changes in conventional spermatic characteristics over the last fifty years (Carlsen et al., 1992; de Mouzon et al., 1996). These changes, both quantitative and qualitative, point to the possibility of an increase in male factor infertility in the younger generations.

After describing the data collection systems on assisted conception in France and the rest of the world, this article analyses the medical treatment for male factor infertility in the different techniques of medically assisted reproduction. On the one hand, in vitro fertilization has very low success rates in cases of severe male factor infertility (this technique having originally been developed to treat female factor infertility). On the other hand, success rates with artificial insemination by donor are satisfactory but the couple has to accept the use of donor sperm. The choice between these two techniques thus made the medical management of male factor infertility problematical until the development of intracytoplasmic sperm injection ten years ago. We shall see that although this new technique has become widely employed, it nonetheless raises a number of questions.

I. Data collection systems on assisted reproduction

The techniques of in vitro fertilization (IVF) were developed as a response to infertility problems. IVF involves retrieving oocytes (by follicular aspiration) and collecting spermatozoa — generally from partners, sometimes from donors — to carry out the fertilization in the laboratory. Once the oocyte is fertilized and has developed into an embryo, it is replaced in the woman's uterus or fallopian tubes. This is how Louise Brown, known as "the first test tube baby", was born in the suburbs of Manchester (England) on 25 July 1978 (Steptoe and Edwards, 1978). France had to wait until 24 February 1982 for the birth of its "first test tube baby", named Amandine, at the Antoine-Béclère Hospital in Clamart (Testart and Frydman, 1982).

1. The diffusion of IVF in France …

The years following the birth of Amandine saw a rapid increase in the number of IVF treatments carried out in France, and around 5,000 "test tube" babies were born annually in the period 1990-1992.

The introduction of this new medical technique brought with it a number of questions. In particular it was felt necessary to evaluate the potential risks to the child and to the woman (Breart and de Mouzon, 1995). Hence it was for reasons both of public health and of research that a prospective survey known as FIVNAT, the National IVF registry(5), was set up in France in 1986 (de Mouzon et al., 1993; FIVNAT, 1993). This survey is based on an exhaustive data collection from the IVF centres that volunteered to take part. Two forms are collected. The "attempt" form describes the infertility assessment of the couple and the progress of the IVF attempt (follicular aspiration, transfer of embryo(s), and whether or not a pregnancy is obtained). The "pregnancy" form describes the medical progress of the pregnancy, its outcome and the health status of the child(ren) at birth. Between 1986 and 2000, FIVNAT processed over 340,000 "attempt" forms and more than 29,000 "pregnancy" forms.

In parallel to FIVNAT, a national data collection system was set up to obtain a comprehensive estimate of the number of IVF procedures carried out in France. This system is based on the annual activity reports from the centres, which were initially collected in the context of GEFF (French In Vitro Fertilization Study Group)(6) and are now collected by compulsory reporting to the Ministry of Health(7). The activity reports must also indicate the outcome of the pregnancies resulting from IVF (and therefore the number of children), but this system suffers from a problem of information feedback between the maternity hospitals where the children are born and the IVF centres. In particular, it is thought that the number of births declared in the activity reports is underestimated.

By combining these two sources (FIVNAT survey and annual activity reports of the IVF centres) it is possible to estimate IVF activity in France.

(5) FIVNAT is an association governed by an executive committee elected every two years at the FFER's (French Federation for the Study of Reproduction) conference. Under the supervision of an epidemiologist, Dr Jacques de Mouzon (INSERM), the data coding, verification, processing, and analysis are undertaken at the Kremlin-Bicêtre Hospital (94), by members of the joint INED-INSERM research unit. A report and more specific analyses are published annually. An introduction to FIVNAT and the results generated by this survey are available at the following address: http://perso.wanadoo.fr/fivnat.fr/.

(6) GEFF's reports were published annually in issues 7-8 of *Contraception, Fertilité, Sexualité* between 1987 and 1992.

(7) Law no. 94-654, 29 July 1994 regarding the donation and use of elements and products of the human body for medically assisted reproduction and prenatal diagnosis. Article L. 184-2: "Every establishment or laboratory authorized to perform medically assisted procreation or prenatal diagnosis and any multidisciplinary centre performing prenatal diagnosis is required to present an annual activity report to the Minister of Health, according to the terms set down by the decree of the said Minister. The aforementioned establishments are also required to establish and maintain records, under conditions set out by the decree of the Council of State, relative to the gametes and embryos they are holding."

The activity reports provide an exhaustive account of the number of assisted fertilization cycles performed in France, and the FIVNAT survey is used to measure the success rates (pregnancies, deliveries, children) under the assumption that the centres contributing to FIVNAT have success rates identical to those of centres as a whole. This approximation may result in a slight overestimation of the number of children born by IVF in France, but it can be judged satisfactory in view of the high coverage achieved by the FIVNAT survey, which recorded 92% of the oocyte retrievals performed in France in 1995-1999 (84% in 1986-1999)[8].

Between 1982 and 1999, more than 66,500 deliveries were obtained after IVF treatment, resulting in the birth of over 85,000 children (Table 2)[9]. These figures reflect the high rate of multiple births, with 127-130 children for 100 deliveries (FIVNAT, 1995). The development of IVF is one of the causes of the increase in multiple births. While one in 100 deliveries resulted in twins between 1901 and 1970, by the 1990s this was the case for one in 75 deliveries (Daguet, 2002). The other factors explaining the increase in multiple births are the development of hormone stimulation treatment, better medical management of multiple pregnancies, and, to a lesser extent, the increase in births to women aged 35-39. These high rates of multiple pregnancies have significant consequences for the children as they are associated with a high risk of prematurity and hence of morbidity (Epelboin and Blondeau, 1989; Laborie, 1994a; Dehan, 1998; Olivennes, 2001; Papiernik and de Mouzon, 2002).

2. … and in the rest of the world

What is the situation in the rest of the world? For the past twenty five years, five worldwide reports on IVF activities have been published by the International Working Group on Assisted Reproduction (IWGROAR) and then by the International Committee on Monitoring of Assisted Reproductive Techniques (ICMART). They report activity in several dozen countries for 1989, 1991, 1993, 1995 and 1998[10]. The last worldwide report was partly based on information supplied by three existing regional registers: the European register, the register for Australia and New Zealand, and the Latin American register. In all, about forty countries participated in the 1998 report and 59% of them reported their activity in full.

IVF treatment is performed chiefly in developed countries. However, the World Health Organization recently received a request for advice on the

[8] FIVNAT's coverage rate was 61% in 1986, the first year of data collection and reached 94% as of 1993.

[9] The retrievals reported in Table 2 are those performed during conventional IVF but also ICSI (see below).

[10] These reports were published in the proceedings of the conferences at which they were presented: the world conferences on "In Vitro Fertilization and Assisted Reproductive Techniques" for the reports of 1989 (Paris, France, June 1991), 1991 (Kyoto, Japan, September 1993) and 1997 (Vancouver, Canada, May 1997) ; the world conferences on "Fertility and Sterility" for the reports of 1993 (Montpellier, France, September 1995) and 1998 (Melbourne, Australia, November 2001).

TABLE 2.– MEDICALLY ASSISTED FERTILIZATION IN FRANCE, 1982-1999 (ESTIMATES)

Year	Authorized centres	Cycles[a]		Clinical pregnancies[d]	Deliveries[d]	Children[d]
		Retrievals[b]	FER[c]			
1982-1985[e]	–	12,000	–	1,400	900	1,000
1986	55	11,779	–	1,767	1,413	1,838
1987	92	18,617	1,409	3,252	2,370	3,065
1988	121	23,143	1,840	4,251	3,124	4,040
1989	115	25,648	2,137	4,841	3,489	4,511
1990	130	27,963	2,682	5,578	4,055	5,239
1991	109	27,498	2,827	5,174	4,007	5,178
1992	102	26,063	2,728	5,172	3,792	4,893
1993	95	26,140	2,784	5,660	4,082	5,269
1994	97	28,920	3,478	6,069	4,639	5,989
1995	101	33,000	4,194	7,007	5,173	6,661
1996	88	35,325	5,173	8,425	6,158	7,890
1997	94	38,752	6,686	9,345	6,925	8,797
1998	96	39,800	7,000	9,617	8,187	10,331
1999	96	41,000	7,500	10,808	8,462	10,675
Total[f]		415,648	50,438	88,366	66,776	85,376

[a] The number of cycles (oocyte retrievals and FER) come from the centres' activity reports. These reports were initially prepared in the context of the GEFF survey (French In Vitro Fertilization Study Group) and are now collected through compulsory statements to the Ministry of Health. The first reports were published in the journal *Contraception, Fertilité, Sexualité*. The unpublished data were supplied by Dr Jacques de Mouzon (INSERM), who is responsible for preparing the annual reports.
[b] Retrievals performed in the context of any medically assisted fertilization technique, the two most important being conventional IVF and ICSI (intracytoplasmic sperm injection).
[c] FER=Frozen Embryo Replacement. During an IVF attempt, some of the embryos may be frozen for transfer in a future attempt. Freezing of embryos is offered particularly when the number of embryos obtained exceeds the number transferred.
[d] The number of pregnancies, deliveries, and children indicated in the centres' reports are underestimated since a proportion of the pregnancies were lost to observation before coming to term. From 1986, the numbers presented here are an estimate based on the hypothesis of a success rate in France identical to that observed in the FIVNAT survey. For example, in 1990, a pregnancy rate per retrieval of 18.7% was observed in FIVNAT, and a pregnancy rate per FER of 13.0%, which gives an estimate of the number of pregnancies in France as: 27,963 retrievals×0.187+2,682 FER×0.130=5,578 pregnancies.
[e] For the 1982-1985 period, it is an aggregated estimate for the 4 years.
[f] For the 1982-1999, period, the 415,648 retrievals performed resulted in 81,445 pregnancies, 62,022 deliveries, and 79,815 children. The 50,438 FER resulted in 6,921 pregnancies, 4,754 deliveries, and 5,561 children.

setting up and use of assisted reproductive techniques (ART) from developing countries where ART is provided mainly in private clinics (Vayena et al., 2002). Some developed countries have experienced a very rapid growth of IVF in recent years. In Japan, for example, between 1995 and 1998, the number of IVF centres increased exponentially, from 96 to 425. As a result of this large increase, Japan carried out more than 53,000 retrievals in 1998, placing it between the United States, which carries out the most (over 60,000), and the three main European countries (France, Germany, United Kingdom), which each carried out 40,000 retrievals in 1998. Europe is by far the continent where recourse to assisted fertilization is greatest.

3. Use of IVF in Europe

In Europe, the European Society for Human Reproduction and Embryology (ESHRE) proposed in 1999 a programme to centralize the data on IVF from the information collected in individual countries. This programme has already resulted in the publication of two reports, for 1997 and 1998 (Nygren and Andersen, 2001a and 2001b). In 1998, eighteen countries took part in the programme (Table 3). However, only nine countries supplied exhaustive data, for although northern Europe has comprehensive national registers, this is not the case for southern and eastern Europe, while western Europe is split between these two groupings. In addition, the authors of the report noted a variability in the quality of the reported data (widely varying coverage rates, different rates of pregnancies lost to observation with countries such as Switzerland where information on deliveries and children remains very fragmented, differences in definitions between countries, etc.). Faced with these difficulties, the European Consortium is currently working to improve the data collection system; at the time of writing, a comparative analysis of the progression of IVF in Europe remains a difficult exercise.

It is possible, however, to estimate a range of values for the number of cycles performed in the countries for which comprehensive data are lacking (Table 3). For these countries, the number of cycles recorded forms the lower limit of the number of cycles performed; moreover, we make the assumption that the centres not included in the report have levels of activity identical to those of the centres that were. This probably leads to overestimating IVF activity (in particular for those countries with a low coverage rate, such as Spain) and this estimate is taken to be the upper limit of the number of cycles performed. Dividing the number of cycles thus estimated by the number of women aged 15-49 in each country, gives an indicator for the rate of recourse to IVF. This rate varies between 1 (in Russia) and 66 (in Denmark) per 10,000 women of childbearing age. In France, the rate of IVF use is 32 cycles per 10,000 women of childbearing age, which is close to that observed in the Netherlands, Finland, and Norway. In Germany, Switzerland, and the United Kingdom the rate of

IVF use is lower (in the region of 23 to 28 per 10,000), while in Belgium, Denmark, Sweden, and Iceland it is higher (over 40 per 10,000).

By adopting a similar approach, it is possible to estimate a range of values for the children born after assisted fertilization as a percentage of all the children born in each country (Table 3). In 1999, 1.4% of children were born after assisted fertilization in France. The percentage of children born through IVF is strongly associated with the number of cycles performed per 10,000 women (Figure 1a): this percentage increases by 1% when the number of cycles performed per 10,000 women of childbearing age increases by 20 units.

The variations in recourse to IVF between European countries raises the question of the reasons for such differences. A first possibility is to attempt to explain "simply" the variations in IVF use on the basis of each country's characteristics. In this perspective, it could be thought that development of the practice is correlated with the country's fertility dynamics, whereby a population wishing to have children would perhaps be more likely to use IVF. Figure 1b shows the variations in IVF use in relation to the total fertility rate (TFR): the association appears tenuous. The use of IVF could also reflect the sterility problems experienced in a population, but no indicator exists for measuring the level of sterility directly[11]. In historical cohorts, the rate of permanent sterility was no doubt linked to the level of involuntary infertility. This rate was relatively stable up to the cohorts born during the 1960s, but increased greatly in subsequent cohorts, as it came to reflect not only involuntary infertility but also voluntary infertility (Sardon, 2002). Table 3 indicates the rate of permanent sterility for the 1955 cohort, which we assume to be strongly associated with the level of involuntary infertility. Once again, no clear association is seen between this rate and the frequency of IVF use (Figure 1c). Other explanations can still be imagined, in particular involving economic considerations, such as the level of health care expenditure (Table 3). But this explanation appears to be no more pertinent than the previous ones (Figure 1d). These first elements do not therefore add to our understanding of the pattern of IVF use in Europe. For further progress in this area, it might be useful to study the conditions of infertility treatment in European countries, for example, by examining the economic cost to couples of IVF (according to whether or not it is paid for by social security systems which vary markedly between countries[12]), the availability of in vitro fertilization (the level of expertise

[11] For demographers the notion of sterility is the opposite of fecundity, signifying the ability to conceive and have a full-term pregnancy (Leridon, 1981). To measure the level of sterility in a population, demographers have suggested using an indirect indicator: the level of involuntary infertility, i.e. the percentage of married women remaining involuntarily childless.

[12] For example, the authors of an article analysing the economic implications of medically assisted reproductive techniques (Garceau et al., 2002) point out that the cost of IVF treatment is fully reimbursed in France and partially so in Belgium, Denmark, and Norway. The United Kingdom is characterized by a large regional variation in public funding; on a national level only one in four IVF treatments are publicly funded.

TABLE 3.– MEDICALLY ASSISTED FERTILIZATION IN 18 EUROPEAN COUNTRIES, 1998 (ESTIMATES)

Country	% of centres recorded	Number of cycles[a]	Number of cycles per 10,000 women aged 15-49	% of children born by assisted fertilization[b]	Total fertility rate (children per woman)	Permanent sterility rate of the 1955 cohort	Health expenditure per head in 1998 (PPS)[c]
Southern Europe							
Spain	38%	8,771 – 23,124	9 – 23	0.5 – 1.3	1.16	9.2	1,194
Greece	44%	6,973 – 15,689	27 – 60	1.6 – 3.7	1.29	8.6	1,198
Italy	~ 54%	13,341 – 24,706	9 – 18	0.5 – 1.0	1.17	12.7	1,824
Portugal	Unknown	1,217 – ?	5 – ?	0.1 – ?	1.46	9.7	1,203
Eastern Europe							
Hungary	75%	2,094 – 2,792	8 – 11	0.5 – 0.7	1.33	8.5	–
Czech Republic	93%	7,879 – 8,442	30 – 32	1.9 – 2.1	1.16	6.2	–
Russia	63%	4,514 – 7,222	1 – 2	0.1 – 0.1	1.24	–	–
Western Europe							
Germany	~ 85%	46,132 – 54,565	23 – 28	1.1 – 1.3	1.36	–	2,361
Belgium	66%	9,847 – 14,985	40 – 61	1.7 – 2.7	1.60	15.2	2,050
France	100%	46,800	32	1.4	1.75	8.3	2,043
Netherlands	100%	13,865	35	1.4	1.63	16.9	2,150
Switzerland	100%	4,002	23	1.0	1.47	–	2,853

Country	% of centres recorded	Number of cycles[a]	Number of cycles per 10,000 women aged 15-49	% of children born by assisted fertilization[b]	Total fertility rate (children per woman)	Permanent sterility rate of the 1955 cohort	Health expenditure per head in 1998 (PPS)[c]
Northern Europe							
Denmark	100%	8,409	66	3.0	1.72	12.9	2,132
Finland	100%	7,547	31	2.6	1.70	15.5	1,510
Iceland	100%	383	54	3.9	2.04	–	2,113
Norway	100%	3,643	34	1.7	1.81	13.5	2,452
United Kingdom	100%	33,647	24	1.1	1.71	–	1,510
Sweden	100%	8,381	42	2.4	1.50	12.8	1,732

[a] This is the total number of cycles performed in the course of IVF, ICSI, and FER. The ranges are estimates: the lower limit is the number of cycles given in the report, the upper limit is the number of cycles estimated on the assumption that the centres not reporting have activity levels identical to those of the centres in the report.
[b] The estimated number of children born after IVF, ICSI, and FER from a cycle performed in 1998 has been divided by the number of children born in 1999. The number of children born after IVF, ICSI, and FER has been estimated from data on the number of deliveries and on the distribution of multiple pregnancies (data provided in the European report). Information on the pregnancy outcomes was lacking for the Netherlands and Belgium, and of poor quality for Switzerland. For these three countries, the number of children born after IVF, ICSI, and FER has been estimated by assuming that these countries have success rates identical to those of the other 15 countries. This assumption has also been applied to Spain to estimate the number of children by FER as this country was missing (without any explanation) from some of the tables in the European report. Furthermore, the European report suffered from inconsistencies in the data for the United Kingdom and consistency assumptions have been made for this country.
[c] PPS (Purchasing Power Standard) is a unit of account independent of national currencies. The conversion of expenditure into PPS enables volume comparisons to be made.
Sources: *European Report on In Vitro Fertilization 1998* (Nygren and Andersen, 2001b), Observatoire démographique européen, *Eurostat Yearbook 2002* and *Bilan démographique des pays développés* (Sardon, 2002).

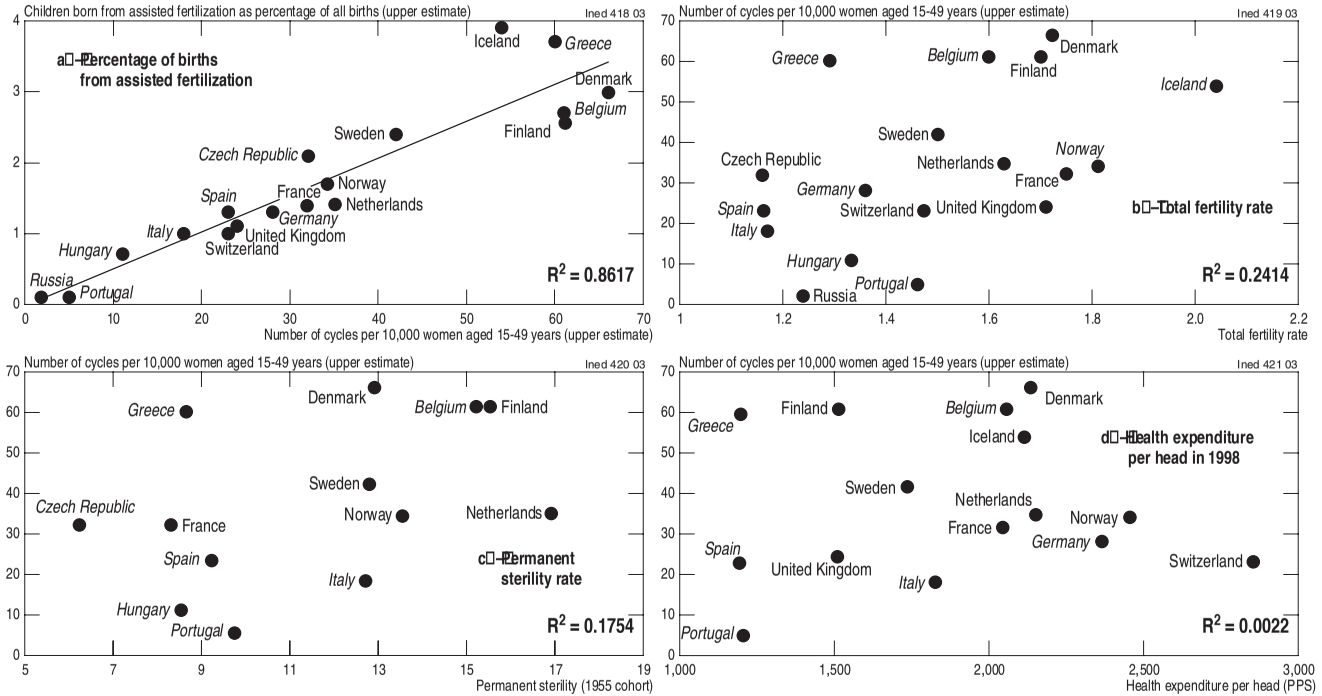

Figure 1.– Use of assisted fertilization (measured by the number of cycles per 10,000 women aged 15-49 years) and demographic and economic indicators

Note: The countries in italics are those for which IVF activity is not known in full and is therefore based on an upper estimate (see Table 3).
Sources : *European Report on In Vitro Fertilization 1998* (Nygren and Andersen, 2001b), Observatoire démographique européen, *Eurostat Yearbook 2002* and *Bilan démographique des pays développés* (Sardon, 2002).

of the health professionals responsible for gynaecological care, the number, size and distribution of IVF centres in the country), or by exploring how well these methods are accepted by the population. The financial cost to couples could be a determining factor. Thus in the United Kingdom, the decision to attempt a second IVF treatment after an initial failure seems to be determined not only by perception of its expected success (a perception based on factors such as the woman's age, the number of oocytes retrieved and the number of embryos transferred during the first IVF attempt) but also on the couple's ability to pay for the treatment in a context where public funding of IVF is extremely limited and variable (Sharma et al., 2002).

II. IVF: a technique poorly adapted to severe male factor infertility

1. Measuring the success of IVF treatments

In the literature, the measurement of the IVF success rate is generally based on the percentage of attempts that have permitted an oocyte retrieval leading to a clinical pregnancy, known as the pregnancy rate per retrieval. From FIVNAT this success rate is estimated at between 20% and 25%. Thus formulated, measurement of success rates may appear simple; in reality, it involves many difficulties which have been the subject of controversy (Marcus-Steiff, 1990 and 1991; Thibault et al., 1991; Humeau and Arnal, 1994; Marcus-Steiff, 1994a and 1994b; Tain, 2003b). The pregnancy rate per retrieval raises four questions in particular.

First, the population accepted for IVF includes sterile couples, that is couples with zero probability of conceiving without medical assistance, but also subfecund couples, who have a non-zero probability of conceiving "naturally" (Leridon, 1981). To measure the real effectiveness of IVF, it would be necessary to take into account the existence of what have been termed the "false IVF babies" (Marcus-Steiff, 1994a), meaning the babies conceived naturally during the IVF cycle and the babies who could have been conceived naturally during the cycle if IVF had not been performed. In other words, the evaluation of success rates should take into account the probabilities for subfecund couples of conceiving without any medical treatment (Leridon and Spira, 1984; Leridon, 1990).

Secondly, the pregnancy rate per retrieval does not give an indication of the proportion of couples obtaining a live birth, since a proportion of clinical pregnancies end in foetal death (miscarriage, extra-uterine pregnancy, still-birth). To obtain an overall measurement of the success of IVF, it is necessary to estimate the rate of attempts leading to at least one live birth as a proportion of the total attempts in which a follicular aspiration

was practised. This rate is called the "take home baby rate" and stands at between 15% and 20% of retrievals, on the FIVNAT database[13]. An initial approximation of this rate can be estimated from the delivery rate (ignoring neonatal mortality). Looking beyond the take home baby rate, a group of European experts stressed the need for the editorial boards of scientific journals to impose the evaluation of success in terms of a single foetus pregnancy leading to the birth of a healthy child (ESHRE Campus Course Report, 2001). This discussion about success indicators (obtaining at least one live birth or obtaining a single foetus pregnancy leading to the birth of a healthy child) relates to more general debates about "good clinical practice", recommending the prevention of multiple pregnancies by limiting the number of embryos transferred during the IVF cycle (Lambert, 2002).

Thirdly, to determine the real success of IVF, we need to measure the probability of success for the IVF treatment course as a whole (which can include several attempts), not just for individual IVF cycles. Such an approach was recently used in an English clinic with 2,056 couples beginning an IVF cycle (Sharma et al., 2002). These couples were observed until a pregnancy was obtained ($n=879$), or until they abandoned the IVF programme ($n=1,155$) or until they had made four unsuccessful attempts ($n=22$). On the basis of this cohort, the authors estimate that after four attempts, 75% of couples have obtained at least one clinical pregnancy and that 66% have obtained at least one live birth. However, many couples drop out before these four attempts have been made: after each IVF cycle, more than 60% of couples who have not obtained a pregnancy give up. For the cohort under observation, 56% of couples abandoned the IVF programme without having obtained a pregnancy, 1% of couples continued with the treatment up to the fourth unsuccessful attempt, and 43% obtained a pregnancy which in over 80% of cases resulted in a live birth.

Finally, there is marked variation in success rates according to the characteristics of the couple. In particular, very strong effects are observed for the woman's age and the man's spermatic characteristics (Hull et al., 1992). We will develop this point.

2. *Success rates decline as the age of the woman increases*

Figure 2 presents the pregnancy rate per retrieval and the delivery rate per retrieval as a function of the woman's age based on FIVNAT data for the period 1987-1996 (FIVNAT et al., 1990; FIVNAT et al., 1991; FIVNAT et al., 1997). A marked decline in success rates is observed after 35-37 years, with the rate for attempts that result in a delivery dropping from 16.4% at 30 years to 9.3% at 40 years and to 2.8% at 45 years.

[13] If the transfer of frozen embryos is included, the success rate increases by 2-3 points.

Because of this, women aged over 35-37 are put on an emergency protocol that speeds up the procedure. Hence the average time from first consultation to first IVF goes from over a year for women aged under 35 to 6 months for women aged 35 and over, according to a study conducted in the clinical gynaecology department of a French hospital on a cohort of women (n=340) consulting for the first time in 1987 or 1991 (Tain, 2002).

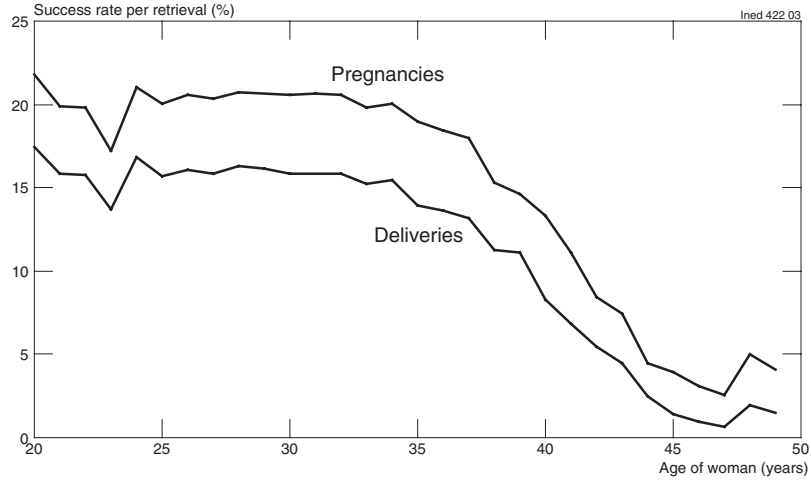

Figure 2.– IVF success rate by age of woman, 1987-1996 (%)
Source: Data from FIVNAT (*Contraception, Fertilité, Sexualité*, 1997, 25(7-8), pp. 503-506, Table 2).

3. Success rates decline when the man has severely abnormal sperm

Success rates also vary as a function of sperm characteristics. IVF was originally developed to combat female factor infertility associated with anomalies in the fallopian tubes but its use has been extended to other female indications and to male and idiopathic indications. The male indications correspond to spermatic abnormalities: in general, a spermogram of less than 20 million/ml spermatozoa and/or less than 40% mobile spermatozoa and/or less than 40% morphologically normal spermatozoa (Plachot, 1987). With this definition, and using the FIVNAT data, the proportion of IVF performed for purely male indications (i.e. in couples where the woman has a normal fecundity) increased from 11% to 22% between 1986 and 1992; over the same period, the proportion of IVF associated with a purely female related factor (usually an abnormality of the fallopian tubes) dropped from 60% to 44%. This increase in male indica-

tions is nevertheless limited by the low success rates for IVF in cases of severe male factor infertility. These failures are related to the lower probability of achieving fertilization in vitro, whereas the probability that the embryos obtained will develop seems not to be affected (Giorgetti, 1987; Tournaye et al., 1992). Thus the fertilization rate (number of embryos obtained divided by the number of oocytes in fertilization) falls from 72% to 18% when the sperm is severely abnormal, i.e. when the proportion of morphologically normal spermatozoa is below 5% and the number of motile spermatozoa is below 3 million/ml (Enginsu et al., 1992).

Given this falling off in success rates, the *Guide des bonnes pratiques cliniques et biologiques en Assistance Médicale à la Procréation* (Guide to good clinical and biological practice in medically assisted reproduction, CNMBRDP, 1999) indicates that the IVF technique should be reserved for men with a minimum of 50,000 motile spermatozoa per millilitre of sperm. What then are the alternatives in cases of severe male factor infertility?

III. AID: a poorly accepted technique

The first response from medical science for cases of severe male factor infertility was artificial insemination with donor sperm. Artificial insemination (AI) consists of introducing sperm into the female reproductive tract (cervical canal, cervix, uterus). The inseminated sperm can be from the husband (AIH) or from a donor (AID). Among couples using AID, four indications are distinguished: azoospermia (complete absence of spermatozoa) in 53% of cases, oligospermia (sperm count below 20 million/ml) in 38% of cases, astheno-teratospermia (reduced percentage of motile spermatozoa and/or of morphologically normal spermatozoa) in 7% of cases, and AID performed for genetic reasons[14] in 2% of cases[15].

1. Deontological rules common to all the French centres

AID has a long history: the first successful AID was performed in the United States in 1884. In 1953, births were obtained using frozen spermatozoa (Netter and Belaisch, 1991). Following on from these technological

[14] AID for genetic reasons is to avoid transmitting to the child a life threatening genetic disorder or one which would cause a severe handicap (a dominant disorder carried by the father, for example). See the *Guide des bonnes pratiques cliniques et biologiques en Assistance Médicale à la Procréation* (CNMBRDP, 1999).

[15] These percentages correspond to the distribution of the indications for AID performed in France in 1984-1987 (*Fédération française des CECOS* et al., 1989).

breakthroughs, the first centres were established in France in 1973, initiated by Professor Georges David, for the freezing and preservation of spermatozoa, and called the Centres for the Study and Preservation of Human Sperm (*Centres d'étude et de conservation du sperme humain - CECOS*). Subsequently CECOS extended its activity to freezing and preserving eggs and embryos[16], and since then the CECOS acronym has stood for the Centres for the Study and Preservation of Human Eggs and Sperm (*Centre d'étude et de conservation des œufs et du sperme humain*). The operation of the French "sperm banks" is unique in that the twenty or so CECOS are organized as a network to form the CECOS Federation[17]. This network makes possible a standardization of procedures between the different centres and the publication of annual national AID reports. As regards procedures, the French system is based on common deontological rules originally established by Professor Georges David[18]: the donor must be consenting, be already a father, and have his wife's agreement; also, the donation is free and anonymous (Madani-Perret, 1987).

2. *Figures for AID in France*

The CECOS Federation collects data on AID and publishes them annually[19]; a report covering the first fifteen years of CECOS' activity (1973-1987) was published in 1989 (Fédération française des CECOS et al., 1989). The first eight years (1973-1980) were characterized by a large increase in couples making a first request, followed by a period of stability with new requests running at around 3,000 a year. The data on AID for the 1986-1998 period are presented in Table 4. In 1990-1992, 20,000 AID cycles were performed each year, resulting in 1,400 deliveries and the birth of 1,500 children.

In contrast to the data collection system set up for IVF, global or European reports are not available for AID. The publication of national AID reports is in fact unique to France, where it is linked to the network operation of the "sperm banks" (Fédération française des CECOS et al., 1989). Without equivalent European- and world-level data, we lack the bases for comparative analyses of this technique.

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[16] Medically assisted reproduction by donation of gametes now includes AID and IVF with a third party donor. IVF with a third party donor can mean a donation of spermatozoa or oocytes, double donation being illegal (Article L. 152-3, Line 1 of the Public Health Code). During an IVF cycle, if the number of embryos obtained is more than the number of embryos transferred, the couple can ask for the embryos not transferred to be frozen with a view to performing a Frozen Embryo Replacement (FER) in a subsequent attempt.

[17] The CECOS Federation has an internet site at the following address: http://amp-chu-besancon.univ-fcomte.fr/cecos/default.htm.

[18] Since 1994, AID activity is covered by the law on bioethics.

[19] Until 1999, the CECOS Federation's report was published in *Contraception, Fertilité, Sexualité*. Since 2000, it is published in *Reproduction Humaine et Hormones*. AID data are also collected for the activity reports produced for the Ministry of Health.

Table 4.– Medically assisted reproduction with sperm donation, France, 1986-1998 (estimates)

Year	CECOS centres[a]	Cycles[b, c]		Clinical pregnancies	Deliveries[d]	Children[d]
		AID	IVF-D			
1986	20	23,926	–	1,938	1,550	1,674
1987	20	23,192	1,408	2,204	1,746	1,939
1988	20	21,446	1,864	2,232	1,762	1,976
1989	20	20,004	2,151	2,186	1,720	1,947
1990	20	20,958	2,329	2,377	1,869	2,095
1991	22	20,190	2,313	2,227	1,746	1,981
1992	22	18,260	2,201	2,219	1,757	2,004
1993	22	17,723	2,146	2,167	1,672	1,908
1994	22	16,887	1,921	2,048	1,610	1,860
1995	22	12,510	1,674	1,620	1,309	1,501
1996	22	10,539	1,254	1,359	1,005	1,165
1997	22	9,735	1,182	1,321	937	1,082
1998	23	8,145	1,294	1,351	859	1,001
Total[e]		223,515	21,737	25,249	19,542	22,133

[a] The CECOS (Centres for the Study and Preservation of Human Eggs and Sperm) were created in 1973. Around twenty in number, they are regrouped in the CECOS Federation which coordinates and harmonizes the operation of the centres, and produces and publishes their annual activity reports.
[b] The cycles are divided into AID and IVF-D. AID (artificial insemination with donor sperm) includes intracervical and intrauterine inseminations. IVF-D (in vitro fertilization with donor sperm) includes conventional IVF, GIFT (Gamete intrafallopian transfer) and ICSI (intracytoplasmic sperm injection).
[c] The number of cycles (AID and IVF-D) are taken from the CECOS centres' activity reports published annually by the CECOS Federation in issue 7-8 of the journal *Contraception, Fertilité, Sexualité* between 1987 and 1999. For 1986-1991, the data relate only to the CECOS centres. From 1992 the report also includes the activities of licensed private clinics, meaning primarily the IFREARES (*Institut francophone de recherche et d'études appliquées à la reproduction et à la sexologie* – Francophone Institute for the Research and Study of Reproduction and Sexology) in Toulouse, which accounts for 1-1.5 % of medically assisted reproduction activity with donor sperm.
[d] The number of deliveries and children are estimated using the hypothesis of an identical success rate for the pregnancies recorded in the report and those lost to observation. Information on the deliveries and the children born is only available from 1990. For the period 1986-1989, the number of deliveries and children born is estimated on the assumption that success rates over this period are identical to those observed over the 1990-1991 period.
[e] For the 1986-1998 period, the 223,515 AID cycles resulted in 19,976 pregnancies, 15,617 deliveries, and 16,916 children. The 21,737 IVF-D cycles resulted in 5,273 pregnancies, 3,925 deliveries, and 5,217 children.
Sources: See notes above.

3. The difficulty of accepting donor sperm

A survey carried out by INED at the end of 1976 made it possible to measure the French population's knowledge of AID at that time. Three years after the creation of CECOS, 79% respondents reported having heard of AID[20], 19% had never heard of it, and 2% gave no answer (Leridon, 1980). Ten years later, virtually everyone (96%) had heard of artificial insemination (Charbit, 1989). But this widespread awareness of AID did not necessarily mean that the technique was well accepted.

AID raises the question of the acceptance or not of the "donor" principle. Two surveys carried out by INED at an interval of eighteen years, in 1976 and 1994, show the state of French public opinion on this subject. In the 1976 survey, the following question was asked: "do you think this [use of AID] is a good solution for a couple determined to have a child and that cannot otherwise have one?". Among those who had heard of AID, 49% answered "no", 41% "yes" and 10% gave no answer (Leridon, 1980). The people opposed to AID were asked about their reasons for rejecting it; three reasons together accounted for 61% of the replies: "it is simpler to adopt a child" (25%), "the child would be only the mother's and not the husband's" (23%), and "the donor might pass on hereditary defects" (13%). These percentages therefore revealed a mistrust of AID in public opinion. However, this mistrust could be explained by the relatively recent creation of CECOS (less than four years earlier) at the time of the survey, and in 1980, when these figures were published, Henri Leridon concluded:

> "It should be noted that this survey is already three years old, and since public opinion changes quickly in this field there is every reason to think that it is now more 'liberal' than two or three years ago" (p. 158).

What was the position eighteen years later, in 1994, in the "Family Situations and Employment" survey (see footnote 1)? Respondents were asked about the medically assisted reproduction methods AID and IVF[21]. After the techniques had been explained to them[22], the respondents were asked whether for a couple unable to have a child it was better to: 1) use IVF or adopt a child?; 2) use AID or adopt a child? The answers are presented in Table 5 according to respondents' sex and according to whether they had experienced difficulties in having a child. Regardless of the respondent's status, IVF is preferred to adoption (49% to 68% in favour of IVF, against 24% to 35% in favour of adoption) but adoption is preferred to AID (49% to 55% in favour of adoption, against 24% to 39% in favour of AID). These responses are revealing of the French population's very different attitude towards these two techniques: by comparing these reports, we can conclude that of the medically assisted reproductive techniques, AID is poorly accepted. Despite the difference of formulation between the 1976 and 1994 surveys, these figures indicate that the French population remains reticent towards AID, probably because of difficulty in accepting the idea of sperm donation.

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[20] After asking the couple about the adoption solution for sterile couples, AID was mentioned in the following terms: "If it is the husband who cannot have a child, it is also possible for the woman to have a child by using artificial insemination (fertilization without sexual relations). Today this can be done with the semen of another man, who will remain unknown to the couple, who receives no payment, and who does it with his wife's agreement and under medical control. Have you heard about this method?".

[21] Unpublished data.

[22] IVF was described thus: "In the laboratory, the woman's ovum is fertilized with the husband's sperm, the embryo is then put back in the mother's womb"; AID was described as follows: "The woman is fertilized with another man's sperm (not her husband's) after an anonymous sperm donation".

TABLE 5.– ACCEPTANCE OF IVF AND AID IN FRANCE IN 1994, BY SEX AND EXPERIENCE OR NOT OF DIFFICULTIES IN HAVING A CHILD (%)

This table presents the responses to two questions*:
1) For a couple unable to have a child, is it better to: use IVF or adopt a child (assuming that the request for adoption would be successful)?
2) For a couple unable to have a child, is it better to: use AID or adopt a child (assuming that the request for adoption would be successful)?

Females:	Have never experienced difficulties in having a child		Have experienced difficulties in having a child	
	IVF	AID	IVF	AID
Use the method	57.5	31.7	66.0	38.5
Adopt a child	31.6	53.3	25.4	49.1
No answer	10.9	15.0	8.6	12.4
	100.0	100.0	100.0	100.0
Males:	**Have never experienced difficulties in having a child**		**Have experienced difficulties in having a child**	
	IVF	AID	IVF	AID
Use the method	49.1	24.6	67.8	32.0
Adopt a child	34.3	54.7	24.0	52.2
No answer	16.6	20.7	8.2	15.8
	100.0	100.0	100.0	100.0

* In introducing these two questions, the interviewer read out a text to explain each method. IVF was described thus: "In the laboratory, the woman's ovum is fertilized with the husband's sperm, the embryo is then put back in the mother's womb". AID was described as follows: "The woman is fertilized with another man's sperm (not her husband's) after an anonymous sperm donation".
Source: INED-INSEE, Family Situations and Employment Survey, 1994.

A socio-demographic survey carried out among 1,041 couples having requested AID during 1985 at the CECOS in Kremlin-Bicêtre (Île-de-France) and in Rennes (Brittany) (Levy, 1994) brings these difficulties into sharper focus. In this group, 43% of the couples abandoned the AID procedure. The reasons for this high drop-out rate are hard to establish since in 57% of the cases the couples broke off all contact with CECOS without giving a reason.

What is the situation in other countries? The law in this field varies from one country to another, with some countries having forbidden or restricted the use of donor sperm (Hamberger and Janson, 1997). In addition, in the countries where sperm donation is permitted, a reticence towards this method has been noted among infertile couples who come up against society's negative attitude towards the method[23] (Mahlstedt and Greenfeld, 1989; Braverman and Corson, 1995). The attitude of close fa-

[23] This negative attitude of society is summed up in the American commander Joshiah Tatnall's famous phrase (1859): "Blood is thicker than water". In particular, a condemnation of AID by the Roman Catholic and Orthodox Jewish religious authorities is observed (Mahlstedt and Greenfeld, 1989). According to Françoise Héritier-Augé, the acceptance of "formulas" such as AID can only occur with the unambiguous support of the law, clear admission into the social structure, and a matching between the collective imagination and the representation of the person and their identity (Héritier-Augé, 1985).

mily members could be decisive, infertile couples being especially concerned about the bond that will link their child born by AID with its grandparents (Mahlstedt and Greenfeld, 1989).

Where differences in attitudes towards AID exist they seem to be associated with the sex of the respondent. Within couples, the decision to begin an AID programme is believed to be taken by the woman in the great majority of cases (Rojo-Moreno et al., 1994; Rojo-Moreno et al., 1996)[24]. In particular, a sharp difference of attitude between men and women is observed over the question of secrecy, men being more likely than women to want to keep the existence of a donor a secret (Braverman and Corson, 1995). It has been assumed that in keeping it secret, men are trying to protect their relationship with the child, which is based on a non-genetic bond. However, this hypothesis may be too simplistic, since a difference in the attitudes of men and women is also observed over IVF with oocyte donation, with men more often than their partners wanting to keep the use of a female donor secret (Braverman and Corson, 1995).

Faced with these difficulties, the medical teams have found that patients need to be given "time to adjust" before starting the AID procedure (Mahlstedt and Greenfeld, 1989). For example, the CECOS team of the Midi-Pyrénées region (La Grave Hospital, Toulouse) considers that once male sterility has been diagnosed it is necessary to wait at least a year before starting AID, to leave the man "time to come to terms with the loss of fecundity" (Mazzone, 2000).

4. AID: a quasi experimental framework for research in human reproduction

AID has also attracted the attention of researchers working in the field of human reproduction. Research in this field suffers from numerous problems, such as selection bias, non-measurable confounding factors, etc. (Baird et al., 1994; Olsen et al., 1998; Weinberg and Dunson, 2000). Given these difficulties, medically assisted reproduction constitutes an original line of approach that enables numerous parameters to be controlled for. It has, for example, been used in the analysis of AID cycles to study the effect of maternal age on fecundity. In the case of AID, the male characteristics (i.e. those of the donor) are randomly distributed among the women: in particular, the donor's age and the woman's age are two completely independent parameters. Moreover, by selecting women whose partner is azoospermic (i.e. has total sterility), a cohort can be formed of women who have no chance of conceiving without medical help, thereby avoiding the problem of selection bias generally encountered in this type of study. Because of these characteristics AID offers quasi experimental conditions

[24] Similar data for the other techniques are not available and so this result is hard to interpret.

for exploring the effect of female age on human fecundity. This enabled two French researchers (Schwartz and Mayaux, 1982) to show that the effect of a woman's age was responsible for a slight decline in fecundity after the age of 30 and a more marked decline after 35. This work confirmed the existing epidemiological and demographic data while specifying the effect of maternal age.

The data on IVF could also be used to study the parameters of human reproduction. Regarding the influence of paternal age, use of data on IVF with donor oocytes or data on IVF among couples in which the woman is totally sterile (i.e. with total bilateral tubal sterility) could be an interesting line of research.

IV. ICSI: the development of a medical response to severe male factor infertility

Between IVF which was ill-adapted and AID which was poorly accepted, the treatment of severe male factor infertility appeared problematic until the early 1990s (Yovich and Matson, 1995).

1. A new technique

In 1992, a Belgian team announced the birth of four babies (including a set of twins) using a new IVF treatment (Palermo et al., 1992). In conventional IVF treatment, an oocyte and spermatozoa are put together, and the spermatozoa have to penetrate the oocyte to fertilize it. The new technique involves taking a single sperm and injecting it directly into the oocyte by means of a micro-pipette. This technique is known as ICSI (intracytoplasmic sperm injection). Within IVF, a distinction is now made between "conventional IVF" and ICSI.

ICSI makes it possible to treat severe male factor infertility, where semen characteristics include very low sperm count, low sperm motility, and abnormal sperm morphology (Mansour et al., 1995; Oehninger et al., 1995). Even with sperm exhibiting major abnormalities, high fertilization rates (number of embryos obtained divided by number of oocytes in fertilization) of around 71% can be obtained using ICSI (Payne et al., 1994). A further step was taken in 1995, when Jacques Testart, the "father" of Amandine, announced the birth of a boy after fertilization of an oocyte with a spermatid, that is an immature sperm cell (Tesarik et al., 1995). Since then ICSI has been used on men whose ejaculate contains no spermatozoa and from whom spermatozoa and sometimes spermatids are retrieved from the testicle, epididymis or spermatic cord(25). According to

the FIVNAT survey, among the children born after ICSI in 1995-1998, 7% were conceived using spermatozoa obtained by surgical retrieval.

At present, therefore, in vitro fertilization encompasses two main techniques: "conventional" IVF, a technique developed to treat female factor infertility; and ICSI, a technique developed to treat severe male factor infertility. Mixed infertility (female and male) can be treated by one or other of these techniques depending on the level of sperm abnormality.

2. The diffusion of ICSI

ICSI has been integrated into the data collection system for IVF. In the FIVNAT prospective survey, 83 ICSI attempts were recorded in 1992. Since 1992, the number of retrievals reported annually by the centres includes those carried out for ICSI. Table 2 thus shows a large increase in the total number of retrievals performed in France, rising from 26,000 in 1992 to 41,000 in 1999. Figure 3 illustrates this development using the proportion of ICSI in the total recorded retrievals between 1992 and 2000: in seven years (1994-2000), the proportion of ICSI grew from 7% to 50%. In numerical terms, this means that of the 41,000 retrievals performed in France during 1999, 18,000 were for an ICSI and 23,000 for a conventional IVF. In parallel with this, a decline in the number of AID cycles is observed, from 17,000 in 1994 to 8,000 in 1998 (Table 4). Figure 4 uses the numbers in Tables 2 and 4 and those in Figure 3 to show the trends in the number of conventional IVF, ICSI, and AID for the period 1986-1999. The rapid development of ICSI between 1994 and 1998 is visible, with a slight decline in the number of conventional IVF and a large decline in the number of AID occurring over the same period. From a purely economic point of view, this rapid and widespread adoption of ICSI to the detriment of AID is paradoxical since AID has a much better cost-effectiveness than ICSI (Granberg et al., 1996; Philips et al., 2000). The question of relative cost-effectiveness receives little attention in France where economic criteria do not enter into a couple's choice, because the cost of infertility treatment is covered by the social security system. The same is not true in every country. Thus in the United States, the cost of ICSI puts it out of reach of part of the population who therefore use AID "by default" (Schover et al., 1996). This has led American physicians to point out that ICSI is responsible for the emergence of a two-speed medical provision in the treatment of male factor infertility (Schover et al., 1996).

(25) The *Guide des bonnes pratiques cliniques et biologiques en Assistance Médicale à la Procréation* (CNMBRDP, 1999) specifies that in the current state of knowledge, the use of spermatids should only be envisaged in the context of clinical research protocols and after approval from the *Commission nationale de médecine et de biologie de la reproduction et du diagnostic prénatal* (National Commission for Medicine and Biology of Reproduction and Prenatal Diagnosis - CNMBRDP).

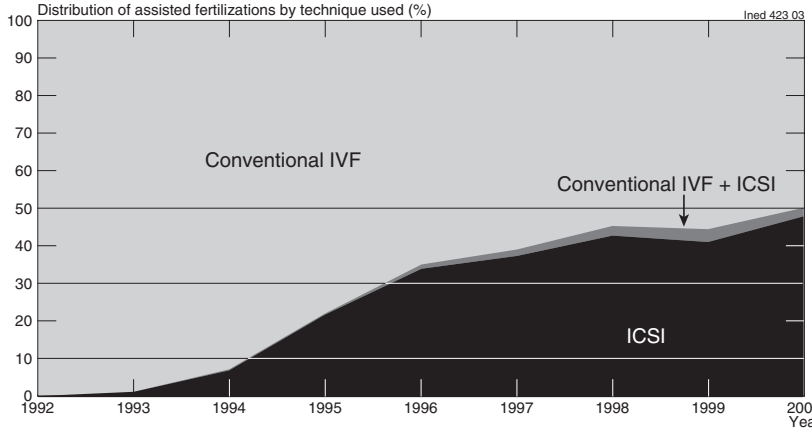

Figure 3.– Proportion of conventional IVF and ICSI among in vitro fertilizations registered in FIVNAT, 1992-2000 (%)

Note: Some centres perform mixed cycles (ICSI + conventional IVF). In this case a proportion of the oocytes are fertilized using the conventional IVF technique, and others using the ICSI technique. According to the *Guide des bonnes pratiques cliniques et biologiques en Assistance Médicale à la Procréation* (CNMBRDP, 1999), these mixed cycles should remain exceptional and be documented in the medical records. Furthermore, if embryos are obtained using both techniques, those obtained through conventional IVF should be transferred first. The embryos obtained through conventional IVF and ICSI should not be transferred simultaneously (unless justified in the medical records), notably because of the need for a correctly documented follow-up of any children that result from this treatment.
Source: FIVNAT.

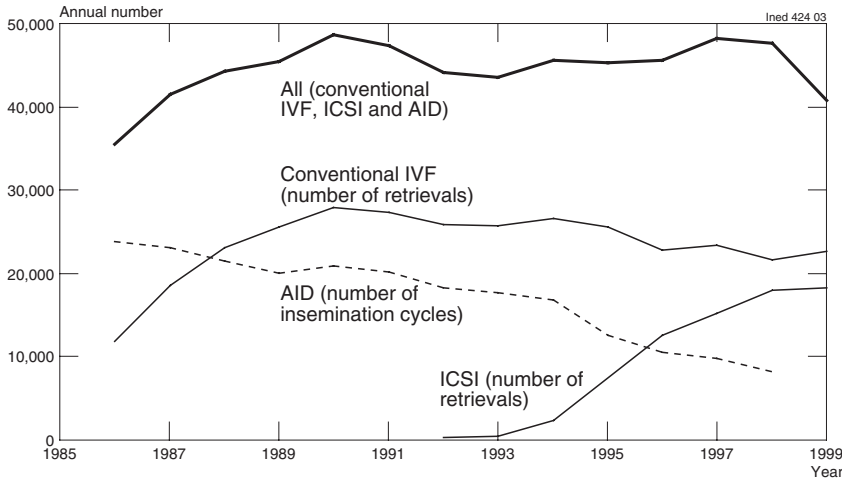

Figure 4.– Numbers of conventional IVF, ICSI, and AID performed in France, 1986-1999

Sources: The annual number of AID (number of insemination cycles) comes from the annual reports of the CECOS Federation. The annual number of retrievals (including both conventional IVF and ICSI) comes from the centres' activity reports. The estimate of the number of conventional IVF and the number of ICSI has been produced by applying the annual proportion of ICSI observed in the FIVNAT survey.

The diffusion of ICSI can be studied at the worldwide level using the 1995 and 1998 reports. Represented in Figure 5 are the twenty countries (or groups of countries) for which information was available in both reports[26]. In 1998, ICSI as a proportion of IVF varies for these countries between 30% and 60%. In six years (1992-1998), therefore, this technique experienced a major growth in the countries taken together, but a high degree of heterogeneity remains: in 1995, the proportion of ICSI ranged from 1% (in Russia) to 51% (in Belgium). In the majority of countries, however, use of this technique has progressed along the same linear trend[27]: in those where the proportion of ICSI was around 20% in 1995 it reached 42% in 1998 (Greece, USA, France, Finland). Some countries diverge from this trend: in Russia and the Netherlands, the proportion of ICSI has increased less, while in Hungary, Italy, and Spain it has increased more. Spain is the most atypical country in this respect, but the large increase recorded is over four years instead of three as is the case for the other countries.

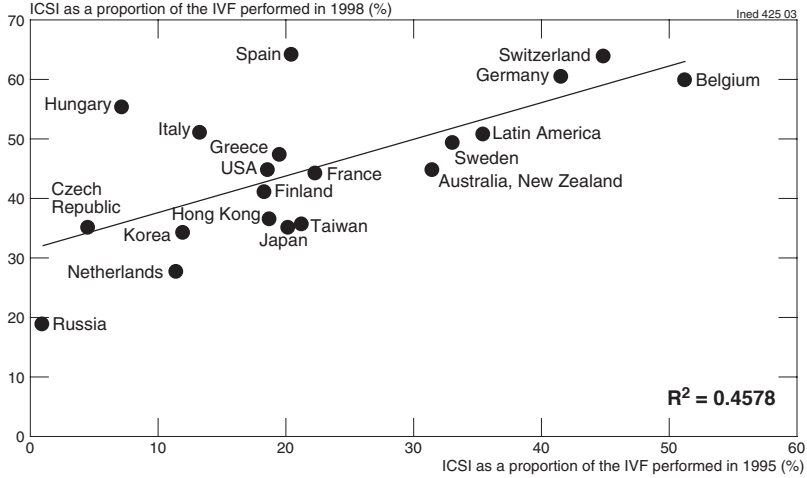

Figure 5.– ICSI as a proportion of the IVF performed in twenty countries in 1995 and 1998 (%)

Source : World reports (see footnote 10).

(26) Only four of these countries or groups of countries reported their activity in full for these two years: Finland, Switzerland, Latin America, and Australia and New Zealand. For the others the proportion of ICSI declared in the centres reporting their activity is assumed to be identical to that of the centres not reporting their activity.

(27) By excluding the five most atypical countries (Russia, Netherlands, Hungary, Italy, and Spain), it is estimated that ICSI use in the other fifteen countries has developed on a line whose slope is given by: proportion of ICSI in 1998 (%)=0.69×proportion of ICSI in 1995 (%)+28.

3. What does tomorrow hold? The medical debate over the diffusion of ICSI

These figures illustrating the rapid and widespread diffusion of ICSI raise questions about the reasons and conditions for the growth of this new technique. From a medical point of view, the use of ICSI is justified in the context of strict indications based on severe abnormality of spermatic characteristics (Khorram et al., 2001). ICSI is also offered when conventional IVF treatment has failed. Nevertheless, the question of the indications for ICSI is the object of a scientific debate in which the European review *Human Reproduction* has taken an active role (Fishel et al., 2000; Hamilton and Bhattacharya, 2001; Ola et al., 2001; Oehninger and Gosden, 2002). This debate sets the supporters of an "all ICSI" position, who advocate extensive recourse to ICSI, even when the man has normal sperm, against the supporters of ICSI use for more restrictive indications (male factor infertility, failure of conventional IVF treatment)[28]. These differences of view could partly explain the cross-national variations in ICSI use. In France, according to FIVNAT data, it is used for male indications in the large majority of cases (71% in 2000), associated or not with female related factors. For the remainder, the authors of the FIVNAT report indicate that these are probably ICSI performed after the failure of IVF attempts.

The supporters of "all ICSI" base their position on research indicating higher success rates for ICSI than for IVF, while the supporters of a more restrictive use of ICSI question the validity of those results by pointing to methodological problems (in particular problems of selection bias). The latter also note the high financial cost of ICSI compared with IVF (around +30%) and stress the need to remain vigilant over a new technique whose consequences have still to be evaluated (Cummins and Jequier, 1995; Patrizio, 1995; Oehninger, 2001; Oehninger and Gosden, 2002).

4. Questions about the health of children born by ICSI

In evaluating the consequences of ICSI, the issue of the children's health is a central concern. This issue had already been raised when IVF was introduced and the same problems linked to multiple births (and the risks of foetal and infant mortality that result) arise in the case of ICSI. But with ICSI three additional questions have to be addressed. Does using

[28] In France, the *Guide des bonnes pratiques cliniques et biologiques en Assistance Médicale à la Procréation* (CNMBRDP, 1999) states that ICSI should be reserved for cases where conventional IVF is impossible or has a very low likelihood of success, particularly in cases of severe male factor infertility. Moreover the *Guide* indicates that ICSI can be envisaged in the case of the failure of conventional IVF. In all cases, the choice of technique and the reasons for it should be set out clearly in the medical records.

severely abnormal spermatozoa carry a risk for the progeny? Does the ICSI technique, which is more invasive than conventional IVF (because the oocyte is penetrated by micro-pipette[29]), increase these risks? Can circumventing the natural process of sperm selection, by choosing a single spermatozoon for the fertilization, have harmful consequences? Several indicators must be used to evaluate the children's health: the risk of congenital malformation, the psychomotor development of the children, and long-term health status. Various "cohorts" of children born by ICSI have been formed in Belgium (Bonduelle et al., 1998 and 2002), in England (Sutcliffe et al., 2001), in Sweden (Wennerholm et al., 2000), in Denmark (Loft et al., 1999), in France (Epelboin et al., 1998), in Australia (Bowen et al., 1998; Hansen et al., 2002), and in the United States. Some studies have obtained reassuring results (Palermo et al., 1996; Bonduelle et al., 1998 and 2002), but others point to a development retardation in children conceived by ICSI (Bowen et al., 1998) and an increased risk of congenital malformation (Kurinczuk and Bower, 1997). Lastly, some authors have put forward the hypothesis of an increased risk of congenital malformation for a number of specific pathologies, in particular those of the genital tract in boys (Wennerholm et al., 2000; Ericson and Kallen, 2001; Sutcliffe et al., 2001), and anomalies in the number of sex chromosomes (In't Veld et al., 1995; Liebaers et al., 1995). These conflicting results reflect the methodological difficulties encountered. These include the small numbers observed (in particular for demonstrating an increased risk of rare congenital malformations[30]), the high rate of children lost to observation, the composition of an adequate case control group, the financial cost of following a cohort of children born by assisted reproduction, ethical considerations concerning the monitoring of a cohort of children, and a heterogeneity in the classificatory systems for malformations (Mitchell, 1997; Hawkins, Barratt, 1999; Sutcliffe et al., 2001; Sutcliffe, 2002). Faced with these questions the *Guide des bonnes pratiques cliniques et biologiques en Assistance Médicale à la Procréation* (CNMBRDP, 1999) stresses that practitioners should inform couples about how little is still known about the effect on children's health and the possible risks associated with ICSI.

Early in March 2002, a study reopened the debate more broadly by concluding that children born by conventional IVF and by ICSI are twice as likely to have a congenital malformation as children born without medically assisted reproduction (Hansen et al., 2002). A few months later, the *British Medical Journal* published an editorial calling for the prompt creation of a large-scale prospective study designed to observe the health of children born by medically assisted reproduction (Sutcliffe, 2002). In

[29] Oocyte damage is observed in around 10% of cases after the injection of the spermatozoon. See the *Guide des bonnes pratiques cliniques et biologiques en Assistance Médicale à la Procréation* (CNMBRDP, 1999).

[30] If a congenital malformation affects 1 child in 1,000, then 20,000 children born by ICSI and 20,000 case control children would have to be observed to demonstrate a doubling of the risk (Hawkins et al., 1999).

France the National Consultative Bioethics Committee (CCN)[31], in its 75th recommendation published in December 2002 (*Comité consultatif national d'éthique pour les sciences de la vie et de la santé* (CNNE), 2002), noted the need for improved evaluation of the consequences of ICSI on children's health but also stressed that establishing a cohort raised ethical problems, with concerns over the risk of stigmatizing the children and respect for individual freedom (requiring follow-up to be based on voluntary participation). The first studies on the health of children born by ICSI will probably look at the risks of congenital malformation and the children's psychomotor development. In the longer term, however, other questions will have to be addressed. Twenty years from now, the first children born by ICSI will be 30 years old. Their fertility will then have to be monitored, with particular attention being paid to the fecundity of boys whose fathers had severely impaired fecundity[32]. Are sons born by ICSI at greater risk of becoming in turn men medically assisted to reproduce?

5. Questions over the health of women

Questions have also been raised about the consequences of ICSI for women's health. In reality, at issue here is the technique of in vitro fertilization in general, be it conventional IVF or ICSI (Laborie, 1994b). In the context of ICSI, however, the concern is over the ethics and consistency of a medical treatment in which the risks of the technique are borne by the woman, even though her own fecundity is unimpaired and the infecundity comes from her partner (Athéa, 1990). Although the issue of treating male factor infertility in the woman's body[33] arose with AID, the potential health consequences for the woman are greater with ICSI, and so too are the questions raised. It is interesting to note that the spouses of infertile men, even when they are aware of these risks, show the same preference for ICSI as the men when required to chose between ICSI and AID[34] (Schover et al., 1996).

Where women's health is concerned, the issue of mental health must also be addressed. Infertility is a source of deep psychological distress and studies have shown that in this area the dominant factor is not the contribution of the individual to the infertility problem (female factor and/or male factor infertility) but the sex of the individual (Greil, 1997). Even in

[31] *The National Consultative Bioethics Committee* (CCN) has a website where these recommendations are published: http://www.ccne-ethique.fr

[32] This issue arises more specifically in the case of male infertility, since it is thought that this may be of mainly genetic origin, transmitted by the father but also by the mother (Meschede et al., 2000; Ford, 2001). The birth of children from infertile men by medically assisted reproduction raises questions over the transmission of this infertility to the next generation.

[33] This relationship between the body (particularly the female body) and assisted medical reproduction techniques has been the subject of sociological analyses (Rouch, 1995; Oudshoorn, 2000; Tain, 2003a).

[34] However, women more often than their husbands mention concerns about their health (Schover et al., 1996).

cases of male factor infertility, women experience greater psychological distress than their partners. The burden of the techniques (AID, IVF and ICSI) falls mainly on women and could be a determining element in explaining this greater female distress (Wright et al., 1991). Other explanations, more sociological, have also been put forward, with the hypothesis that reproduction is still the domain of women (Héritier-Augé, 1985; Wright et al., 1991), even though we now know that infertility is not always due to female related factors. Lastly, in this area of mental health, managing a chronic stress such as infertility apparently differs by sex. Women tend to respond to it by "brooding" on the situation (thus developing reactions of stress and distress), while the reaction of men is to ignore and deny the problem by becoming involved in other fields (Wright et al., 1991).

Conclusion

For a long time, the medical profession considered that the treatment of male factor infertility was limited, particularly compared with the success achieved with female factor infertility (Hamberger and Janson, 1997). In cases of severe male factor infertility, the use of donor sperm was initially the only effective technique of medically assisted reproduction. With the development of ICSI, a revolution in the medical treatment of male factor infertility has thus been observed over the last decade. An infertile man can now conceive a child in vitro that is genetically his. The rapid and widespread diffusion of ICSI reflects the success of this medically assisted reproduction technique developed to treat male factor infertility, but its use raises a number of questions. Its limitations are economic (the high cost of ICSI), ethical (treatment of male factor infertility in the woman's body) and health-related, with in particular questions over both the long- and short-term health of the children born by ICSI. In the face of these issues, we need to remember that other medical revolutions could dramatically alter the medical approach to male factor infertility in the future, at the level both of diagnosis and of treatment (Ford, 2001).

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LA ROCHEBROCHARD Élise de.– **Men Medically Assisted to Reproduce: AID, IVF, and ICSI, an Assessment of the Revolution in the Medical Treatment of Male Factor Infertility**

In response to involuntary infertility, which affects 15% to 20% of couples, the techniques of in vitro fertilization (IVF) have been developed. Between 1982 and 2000, 85,000 children were born in France thanks to IVF (estimates based on combined analysis of the FIVNAT survey and administrative data). Five world reports and two European reports have been produced on IVF, but their use remains limited by incomplete data for regions such as southern and eastern Europe. The success rates with IVF are around 15% to 20% of pregnancies obtained per retrieval. However, these rates decline rapidly as the woman's age rises and when the man's sperm has severe abnormalities. In cases of severe male factor infertility, artificial insemination by donor (AID) was for long the only medical solution, but it raises the problem of accepting sperm from a donor. Since 1992, a new IVF technique, intracytoplasmic sperm injection (ICSI) is available. This technique has been widely adopted in France and in many other countries: in 1998 it represented 30% to 60% of assisted fertilizations. Despite this large development, numerous questions remain concerning the consequences of the technique, particularly regarding the short- and long-term health of children conceived by ICSI.

LA ROCHEBROCHARD Élise de.– **Des hommes médicalement assistés pour procréer : IAD, FIV, ICSI, bilan d'une révolution dans la prise en charge médicale de l'infertilité masculine**

Face aux problèmes d'infertilité, qui concernent 15 % à 20 % des couples, on a assisté au développement des techniques de fécondation *in vitro* (FIV). Entre 1982 et 2000, 85000 enfants sont nés en France grâce à une FIV (estimation basée sur une exploitation croisée de l'enquête FIVNAT et des données administratives). Cinq bilans mondiaux et deux bilans européens ont été consacrés à la FIV mais leur exploitation reste limitée par les problèmes de non-exhaustivité des données pour des régions telles que l'Europe méridionale et orientale. Les taux de succès de la FIV sont de l'ordre de 15 % à 20 % de grossesses par ponction. Cependant, ces taux chutent quand l'âge de la femme augmente et lorsque l'homme a un sperme présentant des anomalies sévères. Dans le cas d'une infertilité masculine sévère, l'insémination artificielle avec spermatozoïdes de donneur (IAD) a longtemps été la seule réponse médicale, mais elle pose le problème de l'acceptation d'un donneur de sperme. Depuis 1992, une nouvelle technique de FIV est proposée : l'injection intra-cytoplasmique de spermatozoïde (ICSI). Cette technique s'est largement développée en France et dans de nombreux pays : elle représentait 30 % à 60 % de l'activité de fécondation assistée en 1998. Malgré ce développement important, de nombreuses questions demeurent sur les conséquences de la technique, en particulier quant à l'état de santé à court et long terme des enfants conçus par ICSI.

LA ROCHEBROCHARD Élise de.– **Sobre los hombres que recurren a la asistencia médica para procrear: IAD, FIV, ICSI, balance de una revolución en la respuesta médica a la infertilidad masculina**

Ante los problemas de infertilidad, que afectan entre el 15% y el 20% de las parejas, se ha producido una evolución de las técnicas de fecundación in vitro (FIV). Entre 1982 y el 2000 se produjeron 85,000 nacimientos en Francia gracias a la FIV (estimación basada en una explotación combinada de la encuesta FIVNAT y de datos administrativos). Aunque se han realizado cinco balances del FIV a nivel mundial y dos a nivel europeo, la explotación de tales balances es limitada debido a problemas de falta de exhaustividad de los datos para ciertas regiones, por ejemplo Europa meridional y del Este. Las tasas de éxito de la FIV son del orden del 15 al 20% de embarazos por punción. No obstante, estas tasas disminuyen fuertemente cuando la edad de la mujer aumenta o cuando el esperma del hombre presenta anomalías severas. En casos de infertilidad masculina severa, la única respuesta médica ha sido durante mucho tiempo la inseminación artificial con espermatozoides del donante (IAD), pero tal método requiere la aceptación del donante de esperma. Desde 1992 existe una nueva técnica de FIV: la inyección intra-citoplásmica de espermatozoide (ICSI). Esta técnica se ha desarrollado ampliamente tanto en Francia como en otros países, hasta representar entre el 30% y el 60% de la actividad de fecundación asistida en 1998. A pesar de una evolución tan significativa, todavía existen muchas dudas en cuanto a las consecuencias de ésta técnica, especialmente en cuanto al estado de salud a corto y a largo plazo de los niños concebidos a partir de ella.

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