National Consultative Ethics Committee for Health and Life Sciences

N°75-Ethical issues raised by the development of ICSI

December 12, 2002

Sommaire

Claire Brisset, Défenseure des enfants (Ombudsman for Children) referred to CCNE regarding the potential risks of using Intra Cytoplasmic Sperm Injection (ICSI*) in the framework of vitro fertilisation.

Five specific questions were asked :

1. Is it acceptable to use spermatids to achieve fertilisation ?
2. How should strategies combining ICSI and preimplantation genetic diagnosis be viewed ?
3. Is there any risk of injecting together with the spermatozoon some of its preservation medium?
4. What are the risks of transmitting gene abnormalities, in particular infertility, to the child ?
5. How can specific monitoring programmes be designed for children conceived by ICSI without stigmatising them ?

These important questions have not so far been elucidated. ICSI has never been the subject of parliamentary debate in the context of the bioethics laws of 1994. A decree dated May 6, 1995, simply mentions on two occasions the micromanipulation of oocytes as being one of the ART* techniques, but no provision is made for the evaluation of a possible risk to children conceived by this method.
As regards the clinical development of ICSI, this new possibility of obtaining embryos when there is a major spermatic deficit, served as validation, whereas the animal testing that is normally required before a new therapy is adopted did not actually take place. The very success of the technique, initially offered in the case of male-factor infertility in order to avoid the need for a third party donor[2], raises new issues, such as the possible extension to other indications unrelated to infertility and/or the possible transmission of genetic mutations to descendents.
* (ICSI - Intra Cytoplasmic Sperm Injection)
* (AMP - Assistance Médicale à la Procréation)

A) Medical aspects[2]

1) The ICSI technique

ICSI, i.e. intra cytoplasmic sperm injection, is an in vitro fertilisation technique which has been in use since 1992.
Fertilisation is achieved by the direct injection of a single spermatozoon into the cytoplasm of the oocyte. It can be obtained from fresh or frozen ejaculate, but can also be extracted surgically from the testes using immature spermatozoa, or from the epididymis.
The oocyte needs to be "prepared" to facilitate penetration by the sperm. This preparation includes enzymatic treatment and micro-dissection of the cells which surround the oocyte.

Injecting the sperm therefore bypasses the normal process of interaction with the oocyte which is replaced by the deliberate selection of a spermatozoon for this assisted fertilisation. Selection criteria are size, form, and mobility of the spermatozoon. Although these characteristics do have prognostic value, they cannot of course guarantee - as is for that matter the case for any natural or in vitro process of fertilisation - that the selected spermatozoon is "normal".

2) French IVF and ICSI data

The FIVNAT (French In Vitro National) network has published comparative results for pregnancies achieved by conventional IVF or by ICSI (table for the year 2001).

	Conventional IVF	ICSI
Number of pregnancies	7062	5224
Spontaneous abortions (%)	18,4	17,8
Ectopic pregnancies (%)	3,4	1,6
Medical terminations (%)	0,6	0,7
DELIVERIES (%)	77,8	80
Number	5492	4178
Singletons (%)	72,1	73,7
Multiples (%)	30,9	28,7
Twins (%)	26,3	24,8
Triplets (%)	1,6	1,5
Quadruplets and higher order (%)	0	0
Embryonic reductions (%)	3	2,4
Triplets or quadruplets (before reduction) (%)	4,1	3,7

This table shows, according to its authors, that ICSI pregnancies give rise a little more frequently (but without statistical significance) to births than conventional IVF pregnancies. The spontaneous abortion rate is slightly lower, which is possibly an outcome of the younger age of mothers and of the absence of female-factor infertility. The same is true for ectopic pregnancies, which is probably a consequence of the smaller number of tubal factor infertilities. However, the frequency of multiple gestation is almost identical since the embryo transfer policy is very similar. This may be explained by uterine receptivity which is globally higher in a population needing ICSI for pure male-factor infertility compared to a population treated with IVF without ICSI, and including implantation infertility factors. Such data demonstrates how difficult it is to study ICSI outside the general context of ART.

3) ICSI indications

As noted above, the initial aim of ICSI was to deal with male-factor infertility. Absence of sperm, or very severe sperm deficit in the ejaculate may be due to secretion disorders because of defective testicular production, or excretion disorders because of an obstruction to the release of sperm, or to a mixture of both. Spermatozoa sources for micro-injection into the oocyte are now evolving towards using not just mature spermatozoa from the semen, or the epididymis, or the testes, but also, performed by some rare medical teams, procedures involving spermatozoal precursors. This particular procedure was approved by CNMBRDP* strictly for the purpose of research.

The success rate is quite obviously important in cases of male-factor infertility when IVF without ICSI does not lead to obtaining an embryo (except with injections of immature spermatozoa of which there are not enough for them to be evaluated). Except in the case of male-factor infertility, the success rate compared to conventional in vitro fertilisation has not been confirmed by all of the recent studies : the figures are respectively 24,2 % and 27,7 % for IVF, and 26,1% and 27,9%[3] for ICSI. A randomised trial comparing conventional IVF and ICSI does not evidence any difference in favour of ICSI[4]. The authors' conclusion is that *"ICSI offers no advantage over IVF in terms of clinical outcome in cases of non-male-factor infertility. Our results support the current practice of reserving ICSI only for severe male-factor problems".*

* (CNMBRDP - Commission Nationale de la Médecine et de la Biologie de la Reproduction et du Diagnostic Prénatal) (National Committee for Medicine, and Reproductive and Prenatal Diagnosis Biology).

This impression of success is perhaps at the root of the considerable increase in the number of indications in the last few years, and has resulted in turning the procedure into a routine so that ICSI can respond to a population which hitherto had not been treated or had needed to secure a sperm donation. In fact, in FIVNAT's latest report, in 2000, 50.6% of in vitro fertilisations had been performed with ICSI, as against 35.1% in 1996. This is evidence of both the relative straightforwardness of the procedure and the fact that IVF centres are convinced of the usefulness and safety of ICSI. However, it is difficult to suppose that this increase is due only to male-factor infertility, even though it is known to be of very diverse origin. Besides chromosomal mutations, male-factor infertility can be connected to endocrinous anomalies and above all to a very low fertilisation rate, observed in vitro, i.e. difficult spermatozoal penetration through the ovular membrane.
Originally, ICSI was used exclusively for male-factor infertility due to severe (numerical or functional) deficiency of the sperm, but is now also used to counter infertility generated by genetic disorders such as cystic fibrosis (absence of the vas deferens) or Kartagener syndrome (spermatozoal flagellar akinesia).
Furthermore, ICSI seems to be a possible solution for a whole range of potential indications. The risk of contaminating the sample to be analysed by PGDj with spermatic DNA present in the medium or attached to the zona pellucida, could justify systematic use of ICSI when performing PGD. Reducing the risk of transmitting a viral disorder by systematically adding ICSI onto IVF procedures, which is recommended in some quarters as being the preferred procedure, is still the subject of debate. Also, in the near future, since freezing the oocyte probably detracts from the chances of fertilisation, ICSI would be useful.
Indications, which do not yet exist, involving the selection of an X or a Y spermatozoon after screening would require the use of ICSI, and clearly would raise an ethical issue even though the presence of sex-linked genetic diseases could justify such a course. However, the considerable risk in ethical terms of such an extension of indications leading to selecting the sex of the child for reasons of convenience, is immediately apparent.
There is, therefore, a clear tendency for ICSI to respond to more indications than those initially expected. This extension reinforces uncertainty as regards the future child. The risk of transmission of a genetic disorder cannot leave us unconcerned in the framework of male-factor infertility, and the use of ICSI routinely may raise economic as well as ethical issues. Society has not had an opportunity to discuss the legitimacy of such a course of action.

- PGD - Preimplantation Genetic Diagnosis

4) Repercussions for the child

Because it "bypasses" fertilisation, there has been much concern regarding ICSI-conceived children.
A complete review of the literature was carried out in 2001 by teams in Strasbourg [ML Guénédal et al.], showing that most studies are derived from the considerable activity of the Van Steirteghem group, which did commendable work in establishing early and regular monitoring of ICSI pregnancies in Belgium.

The following information was obtained regarding the risks studied which fall into two main categories.

A) Those linked to the method itself

For example, there is the risk of introducing foreign material into the oocyte (toxin, virus, DNA, particles, etc…) or of trauma to the oocyte caused by perforation which could have an effect on the embryo or the foetus. The literature does not so far provide any publication confirming or refuting such fears for humans. A study on monkeys has however recently mentioned the possibility of lesions to the meiotic spindle. Another study evidenced the incorporation of a fragment of foreign DNA in the embryonic genome after ICSI.

B) The second major group of risks concerns the actual nature of the injected biological material

Male-factor infertility differs from female-factor infertility in that there is a more considerable involvement of chromosomal abnormality in its origins, although in the case of infertility of a couple attributed to the male partner, the presence of female chromosomal abnormalities can sometimes be the real cause of the couple's infertility.

Infertile men are known to be more frequently carriers of chromosome and gene abnormalities. Possible transmission to the child of infertility or of congenital malformation is another kind of risk.

1- Chromosomal abnormalities

1-1 Their frequency is known to be inversely proportional to the level of sperm production

In the general male population, frequency is 0.6% to 1%. It rises to approximately 5% in oligozoospermic men and 10% for azoospermic men. These chromosomal abnormalities may involve their number (Klinefelter syndrome, XXY) or chromosomal macrostructure (translocation, inversion, etc..). The Klinefelter syndrome is characterised by testicular atrophy and sterility, possible disorders at puberty (gynecomastia) and in some cases, mild behavioural disorders. There is no major disability connected to this clinical pattern and it does not generally lead to termination of the pregnancy according to the pluridisciplinary prenatal diagnosis centres officially empowered to propose the possibility of termination .

Correlations between deletions of the Y chromosome and male-factor infertility have been described since 1976. Major deletions leading possibly to impaired spermatogenesis concern a region called AZF (azoospermic factor). These deletions are not specific to azoospermia, and they are also found in severe cases of OAT (oligo asthenoteratospermia). The frequency of micro-deletions in infertile men varies, depending on publications, between 3% and 19%. Informing couples of the possibility of passing this pathology onto their male offspring is therefore an obligation. Many medical teams systematically screen for micro-deletions men wanting ICSI for an "unexplained" spermatogenesis disorder. Worth noting is that the Belgian group who pioneered ICSI, recently performed PGD for the purpose of seeking out Y micro-deletions carried by the father so as to only transfer "healthy" embryos. This kind of selection could not be performed in France because the indications as defined by law for PGD, require the presence of a "disorder of exceptional severity with no known cure at the time of diagnosis", and such a definition does not match up at all with this kind of gonosomal anomaly. The need to follow ICSI with PGD is clearly a trend away from the norm which must be of concern.

1-2- Transmission of these chromosomal abnormalities

In 1995, In't Veld et al. were the first to draw attention in a very alarming study, to the increase of sex chromosome aberrations with ICSI (30%). However, the conclusions need to be qualified since the study was biased by advanced maternal age and above all by an excessively small number of reported cases.

We are presenting hereunder the cumulative data from studies performed from 1991 to 1998, mostly in Europe, reporting the chromosomal anomaly rates in ICSI foetuses. The incidence of chromosomal anomalies is between 0.04% and 3.3%. The percentage of de novo chromosomal aberrations (autosomal and sexual) varies from 0 to 2.9%, and the rate of inherited chromosomal aberrations (compensated or not) from 0.04 to 1.3%.

In results after seven years of experience, Bonduelle et al. noted 2.6% autosomal

anomalies (28/1082) and 0.8% anomalies involving a sex chromosome. These rates are generally higher than the most frequently quoted standards, i.e. 0.92% for autosomal anomalies and 0.19% for sex chromosome anomalies. However, the interpretation given for that increase, particularly as regards sex chromosome anomalies, mainly observed by these authors, has to be taken cautiously, above all because the reference norms concern control group newborns and not foetuses. This note of caution also applies to the French situation evaluated annually by the FIVNAT report : the figure of 0.7% chromosomal anomalies (16/2332) is within the norms mentioned above, but is at least doubled compared to the reference value given by the authors. Furthermore, the risk factors are not constantly matched between the ICSI populations and those quoted from the control registers which were used (FIVNAT, Report for 1997).
A recent Danish study did not in fact note any anomalies for the sex chromosomes, whereas a high rate of total chromosomal anomalies was observed in the 209 foetuses under examination.
The study carried out by Testart et al. has the advantage of being the only French cohort study, and it appears that the only chromosomal anomalies in the ICSI foetuses are those inherited from their parents. Finally, the correlation between the origin of the injected sperm, be it epididymal or testicular, combined with the fact that both sperm and then ICSI embryos are frozen, and the rate of foetal chromosomal anomalies, is not clearly established (FIVNAT, Report for 1998).
2- Congenital malformations
Data concerning the incidence of congenital malformation observed in ICSI born infants is also scarce, and such studies have not always been conducted in parallel with those evidencing chromosomal anomalies. The percentage of major birth defects observed by the end of the second month varies considerably (1.6% and 3.9%).
Bonduelle et al. observed an increase in the percentage of major malformations at the age of 1 year (3.4%), whereas their figures at two months of age (2.3%) are within the above norms.
In France, the percentage of congenital malformations observed for IVF generally[5] is 2.4%, i.e. almost twice as much as that observed for spontaneous pregnancies (FIVNAT, Report for 1997).
Australian and English centres have not noted any increase in major malformation at the age of one year (4.5% and 4.9% respectively) compared to their control population (5% and 4.1%) which is not the case for the percentage of minor anomalies.
Finally, there again, establishing a correlation between the source of injected sperm and the percentage of congenital malformations does not seem feasible. (FIVNAT, Report for 1998).
One of the difficulties in the interpretation of these results, further aggravated by widely divergent norms, is largely connected to the controversy regarding the classification of congenital malformations. For instance, the classification used by Bonduelle et al. - congenital malformations are classified as major when they have functional consequences and/or require surgical remedy, and all others are classified as minor - is more lenient than the Australian definition. Classification of these malformations, observed by these same authors compared to a control population, enabled Kurinczuk and Bower, using their own classification, to contradict the rather reassuring results of the Belgian study. The virtue of this particularly enlightening study, however, is to encourage seeking a consensus and the continuation of such studies.
Since that time, other articles have been published, in particular in the New England Journal of Medicine of March 2002[6].
The Schieve et al. article concluded as follows : *"The use of assisted reproductive technology accounts for a disproportionate number of low-birth-weight and very-low-birth-weight infants, in part because of absolute increases in multiple gestations and in part because of higher rates of low birth weight among singleton infants conceived with this technology".*
The Hansen et al. article concluded as follows : *"Infants conceived with use of intracytoplasmic sperm injection or in vitro fertilization have twice as high a risk of a major birth defect as naturally conceived infants".*
On the whole, these articles probably conclude to the effect that the risk for children is increased. Furthermore, because this is a fairly recently developed technique, long term

consequences have not yet been explored. Recent articles (ref. Journal of Medical Genetics, January 2003, The Lancet, January 2003) mention a fourfold increase of a rare genetic disorder, the Beckwitt-Widemann syndrome, and a sevenfold increase in the risk of retinoblastoma, although the role of ICSI is not clearly evidenced. However, such studies deserve confirmation. Studies cross-referencing IVF and cancer registries in Australia did not reveal more cancers in IVF7offspring.
Consequently, the doubling of congenital malformation, the transmission of sex chromosome abnormalities causing potential sterility, even though evaluation is not easy and numbers are likely to be low, mean that IVF associated with ICSI is a technique which is not totally devoid of risk for children. However, using ICSI in the framework of an IVF procedure should not be excessively criticised because IVF without ICSI increases the risk of early delivery, and therefore of retarded psychomotor development, particularly in the case of multiple pregnancies and multiple deliveries, and also extremely high rates of morbidity and mortality in the case of very premature births. However, ICSI itself cannot be held responsible for these harmful consequences.

3- Genetic Counselling
Since transmission of such chromosomal and genetic abnormalities exist, before consenting to an ICSI procedure, couples will need to be interviewed and a genetic counselling session should be arranged, although they may still decide that their wish to have a child is overriding. Before any ICSI procedure is attempted, a karyotype should be obtained. Although the possibility is sometimes presented of using preimplantation genetic diagnosis after ICSI to investigate genetic anomalies, this is generally not the case.
The risk of transmission to male descendants, which is now confirmed although there will be no reliable quantitative data for another ten years or so, raises the major ethical problem of uncertainty deferred into the future, but this underlying uncertainty is always present in the background of any ART procedure : freezing of gametes and embryos, IVF and specially ICSI, as it is also in the case of any therapy which may affect the germ lines and the reproductive cells. It is important however to note that recent publications by Sutcliffe and Bonduelle, although only short series are involved and they do not go beyond two years, do not reveal in case-control studies any developmental anomalies in the second year of life of children born after ICSI[7].

5) The question of spermatic material

The diversity of ways in which sperm is obtained reveals a tendency to use increasingly immature spermatic material. It therefore seems important at the outset to separate scientific and ethical problems arising when a micro-injection of fresh or frozen sperm is used, and those arising out of more or less mature material collected directly from the testes. The study of the outcome of ICSI with testicular sperm should be the subject of extensive animal testing before it is used for humans, since this is a legitimate application of the principle of precaution. Using immature sperm, in the present state of scientific knowledge, in order to achieve in vitro fertilisation, raises so many uncertainties regarding the future of the children concerned, that this practice is probably not ethically acceptable.

6) PGD and ICSI

PGD and ICSI are intimately connected. Any PGD procedure requires ICSI for technical reasons to avoid DNA contamination. Some opinions are in favour of adding a preimplantation genetic diagnosis to the ICSI procedure to be sure no genetic disorder has been transmitted to the embryo. Should every future ICSI inevitably involve PGD because searching for sex chromosome anomalies should be systematic when there is a high paternal risk situation ? If this were the case, the ICSI ethical issues would be compounded by those raised by PGD which were the subject of CCNE's Opinion n° 72.

B) Legal aspects

- ICSI has not been mentioned specifically in the bioethics laws since 1994, as noted above, whereas its use in France precedes the initial adoption of these laws. Similarly, this surprising silence is to be noted in the decrees of application concerning PGD (published 5 years after the law, and therefore 7 years after the earliest use of ICSI). The decrees make no mention of ICSI, despite the fact that all the preimplantation embryos for analysis are ICSI generated. A single circular in 1999 concerning proper ART practices dwells at any length on this technique.
-PGD through embryo screening because of the use of ICSI, would be outside the parameters authorised by law at this time.

C) Ethical aspects

In the course of discovery and use of the various ART techniques, the hopes of couples are reinforced by increasing medical attention which may put more emphasis on the effectiveness of the technique than on the attendant uncertainties and risks. For these reasons, the Committee in its Opinion n° 42 dated March 30, 1994, on the evolution of practices concerning medically assisted procreation, stressed the need for vigilance. This opinion referred specifically to ICSI, inter alia, and in view of the very rapid development of this technique, made some recommendations : efforts should be made to find an animal model and develop experimental protocols; couples should be informed of the as yet experimental nature of the method; association with techniques involving intracellular co-cultures should be avoided; and finally prospective evaluation protocols should be undertaken.

1) The right to procreate - how far should it go ?

Undeniably, there is a progressive - albeit marginal - trend in the direction of misuse of assisted reproduction at this time, irrespective of circumstances. Medicine must not respond to the wish to procreate at any price, particularly if the price to be paid can turn out to be an existence deliberately deprived of some of its potentialities. To want a child is the most legitimate need in the world. This legitimacy only exists and should only be taken into account if the child is an end in itself, and if the child's own interests take precedence over the sole desire of producing genetic descendants. Questions regarding the right to bear children and the rights of children have already been addressed in CCNE's report, referred to above in the context of the preimplantation genetic diagnosis (Opinion n° 72).

2) Possible risks to the child and the decision to use ICSI

a) Sterility.

Is it acceptable to allow a child to run the as yet unevaluated risk of sterility or of palliative treatment for it ? Can the techniques of reproductive medicine be allowed to increase the risk of transmitting sterility to their descent ? How do you tell a child that he may have to accept an adult life of sterility ? Perhaps the child's very presence in the world implies that sterility. This information must be imparted to him so that he may be honest and fully informed in his relationship with his future spouse, who may herself need to use ICSI. Although most parents prefer to ignore the possibility and defer considering it for another twenty years or more, two ethical issues concerning the child remain : confidentiality regarding the circumstances of his conception, and the possible consequences that this may have for his own descent.

b) Transmission of a chromosomal or genetic disorder

This issue arises not only after IVF plus ICSI : medical advances make it possible for couples suffering from chronic diseases (diabetes, etc…) to produce children without society having any reason - quite justifiably - to object. But to transmit potentially and knowingly a disease is a legitimate ethical problem, even if all the spermatozoa do not generate transmission of the anomaly concerned. Furthermore, such transmission is not limited to

genetic diseases through a mutation. Progress in the management of pregnancies enable women suffering from chronic diseases to produce children safely so that they may be transmitting risks factors which were not hitherto transmissible.

3) Lack of medium and long term evaluation of new technology.

Fertilisation of an oocyte with the aid of immature spermatocytes or spermatids is akin to experimentation with human beings. Results are uncertain and have not been evaluated, and the future of the embryo and of the child is totally unpredictable.
Animal experimentation is now clearly a first pre-requisite before any therapeutic human trial is conducted. By-passing fertilisation using immature spermatogonia could some day lead to research protocols using auto-grafts or even grafts of germinal stem cells. The risk of germinal manipulation would then be very imminent.
The introduction of foreign proteins or other material besides sperm does not so far appear to be a proven source of harmful consequences.

4) Monitoring of children

Because of the risks inherent to IVF, and to ICSI in particular, long-term epidemiological monitoring of children born after the use of such techniques is essential. However, this raises many difficulties.
Apart from practical problems arising out of the cost and organisation of such monitoring, two ethical issues have been raised.
The first is connected to the risk of stigmatisation. The fact that one is included in such a monitoring programme can be seen as proof of some anomaly or, at any rate, some difference compared to other children, whereas parents and next of kin generally prefer that IVF-conceived children should not in any way stand out from others. Revealing the exact circumstances of his conception to a child is a delicate matter, all the more so because the benefit or harm that could befall him as a result is unknown. The kind of data, routine or specific, should not be a particular problem since there would have to be control groups. So-called "normal" individuals should be monitored just like those who have some specific characteristic. No one should feel singular because of monitoring.
The second argument is connected to self-determination. There may indeed be a contradiction between the requirements of an epidemiological study which, to avoid errors of interpretation, must include information on all the individuals in a cohort, and respecting individual free-will by calling on volunteers only to enter in a study.
There is no easy answer to these arguments. Society, which is now confronted with the development of procedures involving varying degrees of risk, which the national health insurance systems support, has a duty to monitor their outcome. The acceptance of such a principle by parents should, for that matter, be encouraged by the conditions of entry into an IVF programme.
Furthermore, the authorities could be blamed for accepting the development of IVF procedures without making certain that they were innocuous. What is done by authorities in the context of medication such as vaccines, should also be possible for other procedures.
The risk of stigmatisation would be limited if the collection of epidemiological data regarding the health of children were systematic and integrated into the general system of health-related data, and not just organised specially for a specific problem.
One last potentially more serious problem could arise according to the results of the monitoring exercise. Should individuals born with the help of these techniques be informed that they may be vulnerable to some specific risk ? Even though the answer to that question is not easy, society has a duty to constantly re-evaluate its own practices, despite the absence of any major cause for alarm to date.

5) Information

Exact and full information provided to parents is the most elementary of ethical demands. But it is not sufficient to absolve the health system from all responsibility.
This information must cover several points :

- Male-factor infertility is associated with a significant number of chromosomal abnormalities, some of which are transmissible while others are not. The couple must be informed of that risk.
- Genetic transmission of chromosomal and non-chromosomal abnormalities may be justification for a prenatal diagnosis or a preimplantation diagnosis. There again, the need to beware of generalisation of PGD must be mentioned.
- Prenatal diagnosis and genetic diagnosis which, for practical reasons are associated with ICSI, are in themselves ethical and economic problems for public health. Forcing a prenatal diagnosis on someone is reprehensible, but so can be refusing to provide it, or not mentioning that the possibility exists.
- The male partner must be informed that in the case of male-factor sterility, systematic analysis for chromosomal abnormalities before ICSI is necessary even though it may complicate the procedure.
- A booklet for the information of women should be systematically distributed so as to offer a pluridisciplinary approach integrating the science of ART specialists, geneticist-paediatricians, and psychologists.

CONCLUSION

The principle of precaution is an exercise in variable geometry ; although it is persistently invoked in the case of environmental or infectious diseases, it is almost never raised in the context of medically assisted reproduction whereas the very fate of a child is at stake. It is precisely in such cases where data is tainted with uncertainty that the interest of the child must prevail over the interest of the parents. The predictable and accepted transmission of a disease is in itself an ethical issue. However, the legitimacy of an attitude which aims to favour the transmission of a characteristic - particularly a negative one - to a child, deserves to be opposed and similarly the role of medicine in these circumstances cannot go unquestioned.
The cost of this technology is not trifling, and one could consider that preferring efficacy to the detriment of the initial indication (i.e. severe azoospermia or oligospermia) is perhaps incompatible with available resources.
The difficulty of ensuring genuine monitoring is a fact, except for studies bearing on a few dozen, or even a few hundred children, and it is also difficult to organise monitoring solely for the benefit of ICSI conceived children, because of the risk of stigmatisation. The complexity of such studies makes it difficult to achieve a true evaluation of the risk of transmission of genetic disease in the short, medium, or long term. There is however, an ongoing European study comparing IVF, ICSI, and natural birth.
In the circumstances, it does appear that ICSI for the time being should be viewed as a last-resort technique and not as first-line treatment if there is a reasonable alternative. The link between PGD and ICSI must be strictly controlled and cannot be left to individual initiative, both for ethical reasons and for reasons of public health policy. This link is presently under the watchful supervision of CNMBRDP and should be subject in future to the control of the Agency that the law provides for.
Procreation at any cost, despite the chromosome or gene abnormalities carried by at least one of the two parents, pledge a child's future and therefore give excessive prerogative to the desire for biological descent compared to the right for a child to be born with the full complement of life's chances.
It may seem naïve to only raise the ethical issue of ICSI after the birth of tens of thousands of children. Society seems to be discovering in this case that scientific innovation has only been sheltered from criticism because of its patent efficacy.
It would however be unwise to portray this technique as exceptionally dangerous for our future. But it is precisely this silence and relative indifference to the development of indications and to the transmission of certain anomalies, which raise an ethical issue.

CCNE does not wish to trigger concern which would not be founded on objective scientific facts, nor does it aim to petition for any kind of moratorium concerning ICSI. It is, however, the existence of certain facts, the discretion that envelops this activity, the growing number of its indications, which make it an obligation to set out some robust markers. It would be reckless to leave to the future the task of making a critical examination of this technique, and all the more so because the spectacular nature of ART advances may sometimes make the child's fate seem a secondary concern.
The shortcomings of public health data in France on this matter are disproportionate with the major role played by ART in French natality. A society cannot just limit caution to medical conditions which are unrelated to ART, and it is also under obligation to provide itself at all times with the tools required to gain the clearest possible information so that its responsibilities regarding future generations can be properly fulfilled.

December 12, 2002

1 - 21 000 sperm donations in 88, 8 000 now.
2 - This section is largely based on two articles in which are to be found many other references. They are an article by F. Olivennes et al., La fécondation in vitro, aujourd'hui et demain, (In vitro fertilisation, today and tomorrow) Médecine-Sciences 2000 16: 316-323, and an article by de M.L. Guénédal et al., Les risques liés à l'injection intracytoplasmique de spermatozoïde (ICSI) (ICSI related risks), Médecine-Sciences 2001, 17: 44-53.
3 - Depending on whether fertilisations are counted per puncture or per transfer.
4 - S. Bhattacharya et al., Conventional IVF versus ICSI for the treatment of non-male-factor infertility : a randomised controlled trial. Lancet 2001, 357: 2075-2079
5 - There is no data specific to ICSI.

6 - L. Schieve et al., Low and very low birthweight in infants conserved with use of assisted reproductive technology, N E J M 2002, 346: 731-737 et M. Hansen et al., The risk of major birth defects after ICSI and IVF, N E J M 2002, 346: 725-730.
7 - Klip H. et coll., Risks of cancer in offspring of women who underwent ovarian stimulation for IVF. Human reprod 2001, nov; 16 (11) : 2451-8.
8 - Sutcliffe AG. et coll. " Outcome in the 2nd year of life after in-vitro fertilization by ICSI : UK Case-Control study, Lancet 2001 June 30; 357 (92-74) : 20.80 - 4

(c) 2002, Comité Consultatif National d'Ethique pour les sciences de la vie et de la santé