Intracytoplasmic Sperm Injection (ICSI)

Indications, cost-effectiveness and risks to children born after ICSI

December 2006

Department of Medical and Surgical Procedures Assessment
Department of Health Economics and Public Health Assessment
Intracytoplasmic Sperm Injection (ICSI)
THE TEAM

This document is based on the HAS technological assessment report “Intracytoplasmic Sperm Injection (ICSI) - Indications, cost-effectiveness and risks to children born after ICSI” (December 2006).

It was prepared by:

- Linda Banaei, MD PhD and Cédric Carbonneil PhD, project managers in the Department for the Assessment of Medical and Surgical Procedures
- with the assistance of Patricia Dargent MD and Marie-Agnès Dragon-Durey MD, report authors,
- under the direction of Denis Jean David PhD, Assistant Head of Department, and Sun Hae Lee-Robin MD, Head of Department.

The health economics assessment was performed by Cécile Fortanier, report co-author, under the coordination of Stéphanie Barré, project manager in the Department of Health Economics and Public Health Assessment, and under the direction of Catherine Rumeaux-Pichon.

The literature search was performed by Emmanuelle Blondet, Gaëlle Fanelli and Mireille Cecchin, researchers, with help from Maud Lefèvre and Pauline David, assistant researchers, under the direction of Frédérique Pages PhD.

Meetings were arranged and secretarial work was undertaken by Mireille Eklo.

Contact details:
Tel.: +33 1 55 93 71 12
Fax: +33 1 55 93 74 35
E-mail: contact.seap@has-sante.fr
1. Aims

The French National Salaried Workers’ Health Insurance Fund (CNAMTS) had noticed a definite increase in the use of intracytoplasmic sperm injection (ICSI) over recent years. It therefore asked the Haute Autorité de Santé (HAS) to assess (i) whether there was good reason for the increase and (ii) what were the effects on the children born after ICSI in view of the invasive nature of ICSI and the absence of physiological selection of a fertilising spermatozoon.

The objectives of this report were to assess:
- the indications for ICSI
- the efficacy and the cost-effectiveness ratio of ICSI
- the risks to children born as a result of ICSI.

2. Assessment method

This technical assessment is based on a critical assessment of the literature and on the expert opinion of members of a working group and of peer reviewers (see Appendix).

The assessment of the indications, efficacy, cost and risks of ICSI was based on a literature review (mainly English and French publications, 1995 – 2006). Each article was analysed using ANAES’ criteria for critical reviews. The scientific evidence was graded as high, medium, or low according to study design.

The criteria used to assess ICSI efficacy covered all stages from fertilisation to birth. The risks of ICSI were compared with those of conventional in vitro fertilisation (IVF) and natural pregnancies using the following criteria: relative mortality rates, multiple pregnancies, premature birth, low growth, major congenital malformations, abnormal psychomotor development, chromosomal, epigenetic and oncological abnormalities, and hospitalisation in an intensive care unit (ICU).

The critical literature review was examined by a multidisciplinary working group of 18 specialists and submitted to 16 peer reviewers for their opinion. Names of working group members and peer reviewers were put forward by specialty societies (andrology, reproductive biology, health economics, genetics, gynaecology, paediatrics, radiology, urology and virology). Specialists in epidemiology, ethics, genetic risk and viral risk were also called upon.

3. Literature retrieved and analysed

In all, 1 405 studies were found and 457 were analysed. Of these, 192 addressed efficacy and cost-effectiveness by indication, as well as the risks of ICSI (1 technological assessment report, 32 institutional or registry reports, 6 guidelines, 6 meta-analyses, 11 systematic reviews, 49 comparative studies, 65 non-comparative studies, and 22 epidemiological studies).

The level of evidence was low in 74% of the studies. ICSI efficacy was addressed in 63% of studies and risks were addressed in 37%. Levels of evidence are shown in Table 1.

The literature review was hampered by the variety of assessment criteria, definitions, and study durations, and by methodological issues in the comparative studies (methodology not described, poor or no randomisation, differing comparators, inadequate statistical power generally due to small sample sizes, no primary end-point, sub-group analysis, comparison of rates expressed with different denominators, etc.). The most relevant efficacy criteria (cumulative rates and birth rates) were rarely reported.
Table 1. Studies by level of evidence

<table>
<thead>
<tr>
<th>Number of studies (%)</th>
<th></th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
<td>Medium</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Efficacy of ICSI*</td>
<td>14 (11.6)</td>
<td>11 (9.1)</td>
<td>96 (79.3)</td>
<td>121 (63.0)</td>
</tr>
<tr>
<td>Risks of ICSI</td>
<td>15 (21.1)</td>
<td>10 (14.1)</td>
<td>46 (64.8)</td>
<td>71 (37.0)</td>
</tr>
<tr>
<td>Total</td>
<td>29 (15.1)</td>
<td>21 (10.9)</td>
<td>142 (74.0)</td>
<td>192 (100)</td>
</tr>
</tbody>
</table>

* Including 7 cost-effectiveness studies and 2 modelling studies.

4. Reported epidemiological and ICSI activity data

The prevalence of infertility in 1989 was estimated at 14.1% in France and 14% in Europe. A French study showed that male infertility accounted for 20% of cases, female infertility for 34%, both sexes for 39%, and that in 8% of cases the origin was unknown.

ICSI is usually used to treat male infertility. Male infertility is mainly idiopathic and related to varicocele secondary to infection, or is immune-related. Genetic causes are less common. The frequency of genetic abnormalities in the spermatozoa of patients with infertility problems may be close to that observed in the fertile male population (10%) or up to 10 times higher (in the opinion of the working group).

Infertility and genetic abnormality rates have not varied significantly in recent years according to epidemiological data and expert opinion (working group and peer reviewers).

Increasing ICSI activity has been reported in France by the European Society of Human Reproduction and Embryology (ESHRE), the French IVF association (FIVNAT), the Agence de la Biomédecine (Biomedicine Agency) and French National Health Insurance, in Europe by ESHRE, and in the United States by the Centers for Disease Control and Prevention (CDC).

The analysis of activity data for France has shown a 3.3% rise in the number of ICSI cycles between 1998 and 2000. This rise was at the expense of conventional IVF, which fell by 5.6%. Health insurance data for 2000 and 2001 have confirmed the increase in the total number of IVF and ICSI procedures performed and coded¹ (53.1% rise in volume and 58% rise in cost). Reimbursements for ICSI began to stabilise in 2003 and remained stable in 2004. Data from the Agence de la Biomédecine for 2002-2004 have shown that the rise in the number of ICSI procedures slowed down while IVF procedures levelled off. ICSI accounted for 22.3% of in vitro fertilisations (IVF + ICSI) in 1995, 48.5% in 2000, 53% in 2002 (FIVNAT data) and 57% in 2004 (Agence de la Biomédecine data).

ICSI use fell for male indications and rose for non-male indications between 1997 and 2002 (FIVNAT). FIVNAT data for 2002 show a tendency for the IVF and ICSI rates to equalise for female and male indications. There has been a slow but steady increase in the age of the women treated with IVF and ICSI.

The recent use of ICSI in pre-implantation genetic diagnosis (PGD) and viral contexts only accounted for 0.5% and 1.6%, respectively, of all ICSI activity in 2004. According to the experts, there has been no significant change in the use of assisted reproduction in a viral context. However, the volume of ICSI activity in a PGD context has been growing by 15% to 20% each year as more diseases are detected by PGD and more information is provided to couples.

According to the working group members, the rise in ICSI procedures in recent years seems to be due to:

- a wider range of indications for ICSI

¹ ICSI was included in the NABM (list of reimbursed procedures) in February 2000.
the fact that ICSI is chosen sooner in cases where sperm quality is moderately affected.

5. Establishing indications for ICSI

Published data on overall efficacy are given in Table 2.

### Table 2. ICSI efficacy

<table>
<thead>
<tr>
<th></th>
<th>ICSI</th>
<th>IVF</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIVNAT data (1998-2002; 71% complete)</td>
<td>80.3</td>
<td>78.4</td>
</tr>
<tr>
<td>- ratio of deliveries to pregnancies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agence de la Biomédecine data (2002-2004; &gt;98% complete)</td>
<td>23.7</td>
<td>22.3</td>
</tr>
<tr>
<td>- estimated mean clinical pregnancy rate per puncture (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- estimated mean delivery rate per puncture (%)</td>
<td>18.3</td>
<td>16.8</td>
</tr>
<tr>
<td>- estimated mean live birth rate per puncture (%)</td>
<td>22.1</td>
<td>20.4</td>
</tr>
<tr>
<td>European data from ESHRE (1998-2002;100% complete)</td>
<td>26.1 - 26.6</td>
<td>24.2 - 25.1</td>
</tr>
<tr>
<td>- clinical pregnancy rate per puncture (%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICSI efficacy and cost-effectiveness could be assessed according to the degree of sperm abnormality after failed IVF and according to the origin of the infertility. Efficacy was reported as fertilisation rates or pregnancy rates, but rarely as birth rates (whatever the denominator).

ICSI efficacy for indications for which the fertilisation and/or pregnancy rate per cycle was reported are shown in Table 3. The fertilisation rate per cycle varied considerably among studies. It ranged on average from 43% for bilateral absence of the vas deferens to 62.5% for obstructive azoospermia. The pregnancy rate per cycle ranged from 21.4% for IVF failures in cases of non-male infertility to 49.5% for bilateral absence of the vas deferens.

### Table 3. Assessment of ICSI efficacy by indication

<table>
<thead>
<tr>
<th>Indication</th>
<th>Variable (per cycle)</th>
<th>Mean (%) (range)</th>
<th>Studies (N/N)²</th>
<th>Level of evidence</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-obstructive azoospermia</td>
<td>Fertilisation rate</td>
<td>51.5 (39-67.8)</td>
<td>10/12</td>
<td>Low</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Pregnancy rate</td>
<td>23.4 (11.3-49.1)</td>
<td>5/12</td>
<td>Low</td>
<td>None</td>
</tr>
<tr>
<td>Obstructive azoospermia</td>
<td>Fertilisation rate</td>
<td>62.8 (51.9-74.5)</td>
<td>7/11</td>
<td>Low</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Pregnancy rate</td>
<td>32.1 (22.1-57.1)</td>
<td>6/11</td>
<td>Low</td>
<td>None</td>
</tr>
<tr>
<td>Bilateral absence of the vas deferens</td>
<td>Fertilisation rate</td>
<td>43</td>
<td>1/2</td>
<td>Low</td>
<td>IVF</td>
</tr>
<tr>
<td></td>
<td>Pregnancy rate</td>
<td>49.5 (47-52)</td>
<td>2/2</td>
<td>Low</td>
<td>IVF</td>
</tr>
<tr>
<td>Moderate oligoasthenoteratozoospermia</td>
<td>Fertilisation rate</td>
<td>58</td>
<td>1/6</td>
<td>Low</td>
<td>IVF</td>
</tr>
<tr>
<td></td>
<td>Pregnancy rate</td>
<td>32.3 (29.7-35)</td>
<td>2/6</td>
<td>Low</td>
<td>IVF</td>
</tr>
<tr>
<td>Failed IVF (male infertility)</td>
<td>Fertilisation rate</td>
<td>59.1 (52-65.6)</td>
<td>4/8</td>
<td>Low</td>
<td>IVF</td>
</tr>
<tr>
<td></td>
<td>Pregnancy rate</td>
<td>27.5 (26-29)</td>
<td>2/8</td>
<td>Low</td>
<td>IVF</td>
</tr>
<tr>
<td>Failed IVF (non-male infertility)</td>
<td>Pregnancy rate</td>
<td>21.2 (14.8-27.7)</td>
<td>2/2</td>
<td>Low</td>
<td>IVF</td>
</tr>
</tbody>
</table>

Seven cost-effectiveness studies and 2 modelling studies were found for cases of severe oligoasthenoteratozoospermia (OAT) (n=2; medium level of evidence), moderate OAT (1 modelling study), varicocele (n=2; medium level of evidence), and post-vasectomy acquired obstructive azoospermia (n=3; medium level of evidence, and 1 modelling study).

² number of studies reporting the variable for each indication / total number of studies for each indication
The working group members defined first- and second-line indications for ICSI on the basis of the efficacy data in Table 2 and their expert opinion:

- **a first-line indication** is when ICSI is performed straight away, in the absence of any existing alternative or after failed IVF;
- **a second-line indication** is when ICSI is performed where poor sperm quality persists despite previous treatment (medical, surgical, sperm collection, etc.), preventing conception by natural means or by AIH or IVF.

### 5.1 First-line indications for ICSI

- **According to the literature data and expert opinion**
  - **Azoospermia and oligoasthenoteratozoospermia (OAT)** \( n=18 \) of which 13 with a low level of evidence): non-obstructive azoospermia (NOA), congenital obstructive azoospermia due to the bilateral absence of the vas deferens (CBAVD), and moderate or severe OAT.
  - The diagnostic criteria used to choose either IVF or ICSI in cases of male infertility vary among centres. The experts agreed that ICSI is indicated where there are:
    - less than 500 000 motile spermatozoa in total after preparation,
    - or more than 500 000 motile spermatozoa in total after preparation, in cases of abnormal morphology and/or survival.
  - The working group members recommended that the following sources should be used in decreasing order of preference: ejaculate sperm, spermatozoa from the vas deferens, from the epididymis and from the testis. It also recommended that spermatozoa be frozen to avoid needless stimulation cycles or even oocyte puncture.
  - **Total failure of fertilisation or reduced \( \leq 20\% \) fertilisation in a previous IVF cycle** \( n=18 \); low level of evidence): the use of ICSI in the event of reduced fertilisation is justified where the cause is male-related, and should be discussed in other cases (abnormal gamete interaction).

- **According to expert opinion**
  - **Antisperm antibodies** \( n=4 \) including 3 systematic reviews): According to the experts, assays to detect antisperm antibodies should be carried out in cases where agglutinates are observed. ICSI may be performed as a first-line procedure if the antisperm antibody level is \( \geq 80\% \) (depending particularly on antibody location and isotype). Below this threshold, the choice of whether to use assisted reproduction will depend on the sperm parameters.

- **Technical indications for ICSI**
ICSI is always used when IVF or insemination with the partner’s sperm (AIH) cannot be performed for technical reasons unrelated to fertility:

- limited availability of straws or deterioration of spermatozoa after thawing if stored or in a viral context, with or without sperm preparation and virus testing
- pre-implantation genetic diagnosis (PGD)
- in a viral context, if the HIV-1 viral load is between 1 000 and 10 000 copies/ml. This indication is currently being reviewed\(^3\).

\(^3\) Draft revision of the Order of 10 May 2001.
5.2 Second-line indications for ICSI

- According to the literature data and expert opinion
  - **Post-vasectomy acquired obstructive azoospermia** (n=4 (clinical), low level of evidence; n=4 (health economics)). The experts recommended repair surgery with sperm storage. ICSI is indicated after failed surgery, after waiting at least 6 months, provided there is no associated female factor.
  - **Hypogonadotrophic hypogonadism** (n=2; low level of evidence). According to the experts, this is the only case where hormone treatment is effective. After treatment, ICSI should only be performed when poor sperm quality persists, preventing conception by natural means or by AIH or IVF.

- According to expert opinion
  - **Varicocele of the spermatic cord** (1 meta-analysis, 1 literature review, 2 health economics studies). According to the experts, the first-line choice is treatment of the varicocele (by surgery or embolisation).
  - **Acquired obstructive azoospermia of the seminal ducts** (n=5; low level of evidence, all causes of obstruction combined): According to the experts, the first-line procedure should be surgical collection of spermatozoa with storage and corrective surgery if possible.

For both these indications, at least 6 months should elapse before assisted reproduction is considered. After treatment, ICSI should only be performed where poor sperm quality persists, preventing conception by natural means or by AIH or IVF. The waiting period may be shorter where there are associated female and/or male factors.

- **Ejaculation disorders** (1 review based on 220 studies with a low level of evidence, 28 of them concerning ICSI): According to the experts, the cause should be treated first (when treatment is available). Every attempt should be made to obtain a sperm sample. If this fails, sperm should be collected surgically. Sperm storage is recommended, whatever collection method is used. ICSI should then only be performed when sperm quality is poor or when surgically collected sperm prevents conception by natural means or by AIH or IVF.

5.3 Conclusion on indications

According to the efficacy data based on published fertilisation rates and to expert opinion, ICSI is indicated especially in cases of male infertility and after unsuccessful IVF. Other indications, including the technical indications of PGD and a viral context, are less common.

No conclusions can be drawn from the available epidemiological and activity data about the significance of the increase in ICSI activity in recent years. It may be due to a wider range of indications and to earlier use of ICSI for moderate azoospermia.

6. Risks of ICSI to children born after ICSI

The risk analysis is based on the literature data and expert opinion. In each case, the number of studies found and their level of evidence are given in parentheses.

---

4 Whatever the cause of infertility, the woman’s age has a negative effect on ICSI efficacy (8 studies). Chronological or ovarian age is not in itself an indication for ICSI, but it may influence the order in which different kinds of assisted reproduction are attempted. ICSI may thus be performed instead of AIH or IVF.
5.4 Multiple pregnancies

As for naturally conceived children, the main risk for children conceived by IVF or ICSI remains the mortality and, above all, the morbidity associated with multiple pregnancies.

No conclusions could be drawn as to whether the risk of multiple pregnancies after IVF and ICSI is different, because of the low level of evidence of the data.

Multiple births are associated with the transfer of multiple embryos. The mean rates of multiple births were 13.4 and 13.6 times higher after IVF (41.5%) and after ICSI (42.2%), respectively, than in the general population (3.1%) (n=3 (high level of evidence), n=8 (low level of evidence)).

For infants born from multiple pregnancies, rates of premature birth, low growth and major congenital malformations after IVF and ICSI were not significantly different from those after natural pregnancies (n=7 including 3 with a high level of evidence).

The increased risks of premature birth and low growth after IVF and ICSI, which are likely to increase the number of stays in intensive care units (ICUs), are associated mainly with the higher rate of multiple pregnancies after these procedures.

5.5 Mortality and morbidity in single pregnancies

The risks of foetal loss and miscarriage are statistically similar for IVF and ICSI, and are related to parental age (n=6; low level of evidence).

No conclusions could be drawn as to whether the risk of morbidity differs between IVF and ICSI, because of the low level of evidence of available data.

Compared with naturally conceived children, infants born after ICSI have an increased risk of premature birth (estimated mean 9.3% vs 6.4%) and low growth (estimated mean 9% vs 4.7%) (n=2 (high level of evidence), n=2 (medium level of evidence); n=9 (low level of evidence)).

The rate of major congenital malformations was higher in children born after IVF and ICSI (estimated means 5.9% and 3.6%, respectively) than in naturally conceived children (n=4 (high level of evidence); n=4 (low level of evidence)). Since such malformations generally require corrective surgery, the number of hospitalisations (especially in ICUs) and of surgical and medical treatments was higher in children conceived by IVF or ICSI.

Large-cohort, long-term 5-year monitoring studies did not report major differences in the physical, cognitive and psychological development of children conceived naturally and those conceived after ICSI (n=7 including 3 with a high level of evidence).

5.6 Genetic, epigenetic and oncological risks

ICSI allows infertile patients with a high frequency of chromosome abnormalities (estimated mean 5.5% vs 0.37% in a population of fertile and phenotypically normal sperm donors) to have children. This may explain the higher frequency of inherited chromosomal abnormalities in children born after ICSI than in the general population (mean 3% vs 0.37%; n=5).

Given the high probability that they will pass on a heterozygotic mutation of the CFTR gene (responsible for cystic fibrosis), parents who carry such a mutation should be offered genetic counselling (expert opinion).

According to the experts, no conclusions could be drawn about the risk of de novo chromosomal abnormalities or about the likelihood of epigenetic disorders or oncological events, in view of their low frequency (n=11, low level of evidence).

---

5 Conditions assigned code Q (00-99) in the International Classification of Diseases (10th revision) (1) and defined by morphological abnormalities, with or without functional consequences or causing death or requiring surgery.
No study has yet assessed the fertility of children conceived by ICSI and the effects on their offspring, since the oldest are only 14-15 years old.

5.7 Specific risks of the ICSI technique

No conclusions could be drawn from available data about any risks that may be related to the ICSI technique or to the use of surgically collected spermatozoa (n=5; low level of evidence).

5.8 Risks of ICSI in a viral (HIV, HCV, HBV) context

No seroconversion in mother or child has been reported after lavage and assisted reproduction (AIH, IVF or ICSI). Combining IVF and ICSI therefore seems to control the risk of virus transmission. Apart from this risk, the risks reported in couples are the same as in any pregnancy resulting from assisted reproduction (IVF or ICSI).

7. Looking ahead

The assessment of ICSI has implications for the treatment of infertile couples, the need for further studies, and the revision of the Order on assisted reproduction in a viral context.

5.9 Management of infertile couples

- Clinical examination of the man and woman
  The guidelines for providing infertility treatment in France need to be updated, particularly as regards the clinical examination each member of a couple should undergo before any attempt at assisted reproduction. These guidelines should be established by a consensus involving all the health professions concerned.

- Semen analysis
  A consensus among the health professions on the definitions used in semenology would be essential for implementing multicentre quality control in semenology laboratories.

- Conditions under which assisted reproduction is covered by National Health Insurance (NHI)

  Amending the conditions under which assisted reproduction is covered
  The restrictions placed on reimbursement for assisted reproduction procedures by NHI may result in couples missing opportunities. They encourage ovarian hyperstimulation, multiple embryo transfer, and the quick treatment of couples irrespective of the indications.
  The experts made proposals for the amendment of the coverage of assisted reproduction, intended for the bodies concerned.

  Favouring single pregnancies when IVF or ICSI is used
  The limited number of attempts that are covered encourages couples to resort to multiple embryo transfer rather than single transfer. Multiple transfer, however, increases the chance of multiple pregnancies, which are known to carry risks. The possibility of letting the couple choose between single and multiple transfer should therefore be considered. The number of attempts qualifying for reimbursement would then depend on the type of transfer.

- Information for couples on the risks of assisted reproduction
  Couples must be given the most up-to-date scientific information on risks. Since the information provided varies greatly among centres, it needs to be updated and standardised, particularly in terms of the risks involved and the monitoring of the infant to be born.
5.10 Further studies required

In view of the generally low level of evidence of the efficacy and cost-effectiveness data, the experts highlighted the need for further studies on

- the effects of embryo freezing on assisted reproduction;
- the efficacy of assisted reproduction, taking into account the freezing of supernumerary embryos (cumulative rates per puncture including the transfer of frozen embryos);
- the impact of the mother’s and father’s ages on the efficacy of ICSI and IVF (by actual age rather than age class);
- the efficacy of ICSI in cases of immunological infertility;
- cost studies comparing ICSI with any alternative technique for each indication;
- epidemiological studies on infertility in France.

The HAS report has highlighted the need to monitor the children born by assisted reproduction techniques, especially ICSI, account taken of the ethical issues raised. It is therefore imperative to

- set up a programme to monitor the children born as a result of assisted reproduction and their offspring (a task for the *Agence de la Biomédecine*);
- carry out properly structured large-scale studies to confirm or refute the trends observed over almost 15 years, particularly regarding the risks of congenital malformations and chromosomal and epigenetic abnormalities;
- carry out studies to assess the risks of using surgically collected spermatozoa.

5.11 Revision of the Order on assisted reproduction in a viral context

According to the draft revision of the Order of 10 May 2001 proposed by the *Agence de la Biomédecine* (currently in the process of being adopted), virus detection procedures should be relaxed (for HIV infection) or abolished (for HCV infection). Detection of HIV-1 RNA in seminal fluid should be maintained, with a treatment threshold set at 100,000 copies/ml."
## APPENDIX - Working group members and Peer reviewers

### Working group members

<table>
<thead>
<tr>
<th>Working group members</th>
<th>Reproductive biologist</th>
<th>Brest University Hospital</th>
<th>Lyon 1 UMR 5205, CNRS Lyon 1, Villeurbanne</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Véronique Amice</td>
<td>Health economist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Professor Jean-Paul Auray</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Jean-Philippe Ayel</td>
<td>Gynaecologist/Obstetrician</td>
<td>Cabinet Médical du Val de Seine, Argenteuil and Hôpital Bichat, Paris</td>
<td></td>
</tr>
<tr>
<td>Dr Pierre Boyer</td>
<td>Reproductive biologist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Nelly Frydman</td>
<td>Reproductive biologist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Professor Clément Jimenez</td>
<td>Andrologist, Developmental and Reproductive Biology</td>
<td>Dijon Complexe Bocage University Hospital</td>
<td></td>
</tr>
<tr>
<td>Dr Lionel Larue</td>
<td>Gynaecologist/Obstetrician</td>
<td></td>
<td>Groupe Hospitalier Diaconesses / Croix St Simon, Paris</td>
</tr>
<tr>
<td>Dr Jacqueline Mandelbaum</td>
<td>Reproductive biologist</td>
<td>Tenon Hospital, Paris</td>
<td></td>
</tr>
<tr>
<td>Dr François Merlet</td>
<td>Reproductive biologist</td>
<td>Saint-Denis</td>
<td></td>
</tr>
<tr>
<td>Professor Philippe Merviel</td>
<td>Specialist in Gyn/Ob and Reproductive Medicine</td>
<td>Amiens University Hospital</td>
<td></td>
</tr>
<tr>
<td>Dr Jean-Marc Rigot</td>
<td>Urologist/andrologist</td>
<td>Calmette Hospital, Lille</td>
<td></td>
</tr>
<tr>
<td>Dr Patrick Thonneau</td>
<td>Epidemiologist</td>
<td>Paule de Viguier Hospital, Toulouse</td>
<td></td>
</tr>
<tr>
<td>Professor Michel Vekemans</td>
<td>Medical geneticist</td>
<td>Necker Enfants Malades Hospital, Paris</td>
<td></td>
</tr>
<tr>
<td>Professor Stéphane Viville</td>
<td>Reproductive biologist</td>
<td>CMCO, Schiltigheim.</td>
<td></td>
</tr>
</tbody>
</table>

### Peer reviewers

<table>
<thead>
<tr>
<th>Peer reviewers</th>
<th>Paediatrician/Geneticist</th>
<th>Robert Debré Hospital, Paris</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Clarisse Baumann</td>
<td>Gynaecologist/Obstetrician</td>
<td>CHI Jean-Rostand, Paris</td>
</tr>
<tr>
<td>Dr Joëlle Belaisch-Allart</td>
<td>Virologist</td>
<td>Saint-Etienne University Hospital</td>
</tr>
<tr>
<td>Dr Thomas Bourlet</td>
<td>Reproductive biologist</td>
<td>Toulouse University Hospital</td>
</tr>
<tr>
<td>Professor Louis Bujan</td>
<td>Reproductive biologist</td>
<td>CHRU, Caen</td>
</tr>
<tr>
<td>Dr Isabelle Denis</td>
<td>Reproductive biologist</td>
<td>Hôpital Bichat Claude Bernard, Paris</td>
</tr>
<tr>
<td>Dr Aviva Devaux</td>
<td>Reproductive biologist/ Medical gynaecology</td>
<td></td>
</tr>
<tr>
<td>Gérard Dürro</td>
<td>Health economist (Methodology)</td>
<td>Université Lyon 1, Umr 5823, Cnrs Lyon 1, Villeurbanne</td>
</tr>
<tr>
<td>Professor Alain Haertig</td>
<td>Urologist, Forensic Medicine</td>
<td>Paris</td>
</tr>
<tr>
<td>Dr Jean Hermabessiere</td>
<td>Urologist (private practice)</td>
<td>Clermont-Ferrand</td>
</tr>
<tr>
<td>Dr Vincent Izard</td>
<td>Specialist in general surgery, urology, gynaecology, obstetrics</td>
<td>Hôpital A. Béclère, Paris</td>
</tr>
<tr>
<td>Dr Philippe Labrune</td>
<td>Paediatrician/Geneticist</td>
<td>Hôpital A. Béclère, Clamart; Paris Sud University UFR, Kremlin-Bicêtre</td>
</tr>
<tr>
<td>Dr Rachel Levy</td>
<td>Reproductive biologist</td>
<td>Saint-Etienne University Hospital</td>
</tr>
<tr>
<td>Professor Stanislas Lyonnet</td>
<td>Genetics</td>
<td>Hôpital Necker Enfants Malades Hospital, Paris</td>
</tr>
<tr>
<td>Dr Aline Papaxanthos</td>
<td>Reproductive biologist</td>
<td>Hôpital Pellegrin University Hospital, Bordeaux</td>
</tr>
<tr>
<td>Professor Claude Sureau</td>
<td>Gynaecologist</td>
<td>Neuilly</td>
</tr>
<tr>
<td>Dr Philippe Verbeq</td>
<td>Radiologist</td>
<td>Clinique du Bois, Lille.</td>
</tr>
</tbody>
</table>

The working group met in January, March and September 2006. Peer reviewers were consulted in August 2006. No working group member or peer reviewer declared a conflict of interest.

---

1 Member of the National Ethics Advisory Committee.
2 Representative of the Agence de la Biomédecine.
3 Medical policy officer at the AP-HP (Group of Paris hospitals).
4 Member of the National Ethics Advisory Committee and of the National Academy of Medicine.