Opinion

Introduction

Growing and pressing demand

In couples in which one partner, either the man or the woman, has been infected by HIV, also called HIV-discordant couples, a growing and pressing demand to found a family is discernible. This development of demand is due to increasing numbers of HIV-positive individuals in this country, and also to therapeutic progress which has prolonged survival and greatly reduced the severity of HIV related pathology.

This Opinion considers the situation where the man is HIV-positive. It was agreed to deal initially with this situation in which there is no direct risk for the unborn child. Circumstances in which the woman is HIV-positive will be the subject of further study in coming months.

The possibility that in the near future AIDS may become a chronic affection, and the fact that society which is aware of these developments sees the disease in a better light, are factors which lead some couples where the man is infected by the virus to consider a positive follow-up to their desire to bear children. Such a decision usually takes place after a period of time during which matures an understanding of difficulties, risks, and consequences of founding a family. For both partners, the symbolic value of the decision is high.

Such a demand appears all the more justifiable because since the beginning of the epidemic, fighting every kind of discrimination in society, the workplace, and the family, has been a priority. The aim was to gain, for those infected by HIV, recognition to equality of rights and obligations identical to those enjoyed by the population at large. In this way, at a time when some individuals are returning to active employment after believing they could never hope to do so again, and more generally when they can at last imagine a future for themselves, denial of parenthood which for a long time was viewed as positive discrimination in order to protect partner and child, now takes on the guise of forcible sterility. It is experienced as an ultimate discrimination against people who have already suffered the throes of learning they were HIV-positive, of awareness of impending death, and sometimes symptoms of the disease and its social consequences. However, consideration must be given with equal measure to the fate of the unborn child.
I. Options now on offer

Within the AIDS prevention effort, there are now four options for couples who wish to have children. An evaluation of sexual transmission risk from a man to a woman remains particularly difficult because it is conditioned by sexual behaviour and by both biological and medical factors. In spite of longitudinal quality studies, statistical data is not easily of use when advising or counselling an individual (11).

Taking into account these uncertainties, up till now only two possibilities were on offer to HIV-discordant couples who wanted a child: adoption or artificial insemination by donor.

1) Adoption

Adoption has not so far been in much demand by sero-discordant couples because it is a cumbersome process (inquiry, interviews, tests), there is a risk of disclosure of the seropositive status of the adoptive father, and there is a long wait. This wait is further prolonged because social services are reluctant to hand over a child to a couple in which one parent is at high risk from a serious disease. Wishing to protect the child, they hesitate to risk exposure to further trauma. In the present state of affairs, these fears may appear excessive.

2) DAI (donor artificial insemination)

Artificial insemination by unrelated donor was developed to respond to conditions of infertility which had little to do with HIV-positive men. In fact, DAI only partially meets the need to have children. It can satisfy couples whose primary consideration is safety. Acceptance criteria by approved medical teams are necessarily stringent so that about half of the couples applying do not meet the criteria and are therefore denied access.

At the present time, although there is still some uncertainty as regards the degree of heterosexual transmission risk, two new approaches are beginning to be offered under the pressure of unsatisfied demand and in a context where the disease is becoming more familiar.

3) Unprotected intercourse during ovulation

The medical approach is very similar to that followed in the case of a sterile couple, including clinical and biological investigation of HIV infection of the male partner, of ongoing treatment and results of that treatment, and a fertility work-up for the couple, but added to this are:

- for the man: sperm analysis and urogenital infection investigation,
- for the woman: hysterography and investigation of menstrual cycle, with ultrasound monitoring of ovulation and HIV serology tests at monthly intervals.

Also, prior interviews with the couple are organised to evaluate existing or foreseeable problem areas.

A recent French study reports 68 conceptions subsequent to unprotected intercourse during ovulation, of which 17 were the result of a single act of intercourse. No case of seroconversion has occurred in the three months following conception (1). However, three women were infected, two of them in their seventh month of pregnancy, and a third some time distant from fertilisation.
4) Intra-uterine artificial insemination with processed and screened spermatozoa from an HIV-positive man

Processing semen in order to eliminate any existing virus brings new hope for sero-discordant couples and fuels increasing demand addressed to physicians. As is the case for unrelated donor insemination, this is an act of medically assisted reproduction in order to avoid the risk of viral transmission.

Until 1995, validation of semen processing techniques was hampered by insufficient sensitivity of screening for the viral genome in its functional RNA form or in its proviral DNA form. The development of techniques able to detect extra and intra-cellular HIV RNA, and intra-cellular HIV DNA, have made it possible to evaluate molecular scale semen decontamination methods. It is now possible to find and quantify the presence of viral genome in the ejaculate, particularly after separation of cells from the seminal fluid. Recent studies have shown that the virus is found essentially in the seminal fluid and non germ cells of semen. However, it seems that the virus may adhere to the spermatozoa. So far, there has been no evidence of any intra-cellular penetration by the virus, nor of any specific receptors on the spermatozoa. Passive fixation of HIV on spermatozoa could be a source of contamination since viral RNA has been found, but no proviral DNA in spermatozoa processed for medically assisted reproductive purposes. However, proviral DNA is only found in the round cells of the spermatic line and in seminal leukocytes when seminal and/or blood viral load of HIV-RNA is high. The correlation generally found between blood and seminal viral burdens presents exceptions which render any individual prognosis worthless and which speak in favour of a systematic analysis of seminal fluid before medically assisted reproduction procedures begin (see annex 1).

It is now possible to assert that removal of spermatozoa from the seminal fluid and related viral investigation are increasingly efficient methods which may not be regarded as totally safe, but do nevertheless reduce very significantly the risk incurred by unprotected intercourse during ovulation. This reduction of the risk of maternal HIV contamination is closely connected to the quality of the clinical environment (ovulation monitoring and mainly intra-uterine insemination techniques) and of the biological environment (medically assisted reproduction, virology, immunology).

The distinctive feature of these "new" possibilities for sero-discordant couples is that they use the sperm of the seropositive man and so enable him to be the biological father of his child and not be excluded from the reproductive event as is the case for adoption and DAI. These two methods therefore would offer a largely positive response to today's unsatisfied demand with the reservation that there is a residual risk of heterosexual transmission which, however small, must be recognised, evaluated, and compared. Furthermore, methods involving unprotected intercourse with ovulation monitoring and artificial insemination with processed and screened spermatozoa from a seropositive male do raise a number of ethical and legal issues since in the first case there is a contradiction with prevailing prevention policies, and in both cases, the medical profession must bear the responsibility of a potentially contaminating procedure.

II. - Reproduction and prevention of HIV

Regardless of which options for founding a family are offered to a couple with an HIV-positive man, the man's future fate must be a primary consideration. The biological and clinical status of his viral infection and his response to treatment must be evaluated.

With adoption and DAI, as the seropositive man is excluded from the reproductive procedure, any risk of transmission to mother or child is excluded by definition.

In the case of artificial insemination with the seropositive partner's processed and screened spermatozoa, the risk of HIV presence (annex 1) is much reduced by various spermatozoal processing methods. A sizable experiment in Italy involved a thousand attempts and 200
pregnancies without a single seroconversion, but viral test results were difficult to interpret (9, 10). A recent French study, with more in-depth viral research, reports only a restricted number of inseminations (12, 13).

In the case of unprotected intercourse with ovulation monitoring, it is not possible to reduce the risk to the same extent as with intra uterine insemination. Furthermore, the French experiment reveals an unexpected risk: three seroconversions at a distance in time from fertilisation. The one-time practice of monitored unprotected intercourse may lead these couples - consciously or otherwise - to take risks in later intercourse.

Another subject for concern is the possibly adverse effect on the general public as regards prevention policies if this possibility for HIV discordant couples becomes known. This partial elimination, with medical approval, of protective practices must not be understood as meaning that the risk of transmission during sexual intercourse is diminished generally, since this could then lead to a general relaxation of alertness and mindfulness of prevention.

Given that the rate of fecundation is about 25 per cent (rate of birth per cycle in fertile couples) repeated attempts will have to be made to achieve pregnancy, thus increasing the risk of transmission.

Medical accountability is committed to a clearly defined and stated prevention policy.

III - Medical assistance - The issues

Both of these techniques raise the problem of whether physicians and scientists should participate in procedures aiming at fertilisation knowing that there is a risk of HIV transmission, however trivial.

Adoption and donor artificial insemination do not present any particular health risk for the child, but artificial insemination with the partner's semen must be considered with care in both its ethical and legal aspects.

The technique seems to be covered by articles L. 152-1 and L. 152-2 of the Code of Public Health (Code de la Santé Publique). This is undeniably medically assisted reproduction by "artificial insemination". Furthermore, the objective is to "avoid transmission to the child of a particularly severe disease", in this case obviously associated to minimising the risk of transmission to the mother.

But there remains in such a situation an element of uncertainty and, in case of failure, the question does arise of whether artificial insemination with the spouse's semen was in fact the vehicle of transmission. In the latter case, the result is the opposite of what was intended.

It is up to the couple concerned to choose, after being fully informed of the following alternatives:

- either the doctor refuses to take action and gives the couple his best advice which in fact adds up to a single recommendation: try and avoid reproduction because there is a risk and you must measure the consequences of contaminating your spouse and giving birth to an infected child.

- or the medical team offers a monitoring of ovulation so as to optimise the fertility of one sexual intercourse, or a medically assisted reproduction effort including processing and viral screening of sperm in an attempt to achieve pregnancy with minimum risk in the present state of scientific knowledge.

Degrees of risk must be compared. On the one hand, there is rejection of childbearing, which does not however protect the couple from unintentional fertilisation nor from denial of
the risk. On the other hand, there is a wish to conceive knowing that there subsists a certain margin of risk which science cannot totally eliminate.

In the first scenario, the practitioner advises but plays a passive role. In the second, he takes part in assisting reproduction and perhaps transmitting a disease, but in conformity with his legal obligation to use all available means, he strives to avoid transmission and gives a hapless pair a chance of joining the ranks of other fertile couples.

However, a comparison by the physician of risks inherent in natural conception with ovulation monitoring, or in artificial insemination with processed semen, should lead him to a preference for the second technique to be offered to couples with all pertinent medical and scientific information.

Such information may be provided by execution of article L. 152-10 included into the Code of Public Health by application of Law n° 94-654 dated July 29th, 1994. This text (see annex 2) in fact prescribes that during medically assisted reproduction procedures, there should be provision for interviews between the couple concerned and members of the medical team and that, if required, social services should also be called in to help.

**Conclusion**

Recent scientific developments concerning AIDS and the biology of HIV as well as progress in available treatment have modified society’s perspective.

This may explain an increasing inclination to refuse enforced sterility which is experienced as being social and medical discrimination, in particular when in the HIV discordant couple, the man is seropositive.

Initiation or resumption of such parental projects forces doctors to choose between two concerns: prevent what cannot as yet be completely cured or respect a couple's choice in a spirit of informed mutual trust. Against this background, to inform a couple on existing possibilities and the risk of viral transmission in each particular medical and psychological situation, is a duty which must fall upon qualified medical teams recognised by the health authorities.

It is also up to such teams to persuade couples to adopt what seems to be the least risky reproductive technique, which to the best knowledge of scientists at present is artificial insemination with processed semen when marital fertilisation is preferred.

Research on the presence of HIV in sperm, on the possibility of passive transport of HIV by spermatozoa, on infective mechanisms, on the effects of therapy on spermatogenesis, and on the evaluation of methods for processing spermatozoa before insemination, should be encouraged and supported more than ever before.

**Recommendations**

The National Consultative Ethics Committee and the National AIDS Council (*Conseil National du Sida*), emphasise the following regarding possibilities now being offered:

- adoption and medically assisted reproduction with the aid of an unrelated donor still remain the safest course for couples unwilling to take any kind of risk of transmission;

- medical monitoring of unprotected intercourse presents an excessive risk of exposure to infection. The Committee and the National AIDS Council are of the opinion that this method should be ruled out because of undesirable secondary effects on risk prevention, mostly for the mother, and because of the contradiction with arguments in favour of strict adherence to protected intercourse put forward by AIDS prevention campaigns;
- intra-marital insemination of processed and screened spermatozoa provided by the seropositive male partner seems to considerably reduce risk because of recently acquired possibilities of evaluating the viral load in contact with spermatozoa in the seminal fluid with sensitive techniques.

The National Consultative Ethics Committee and the National AIDS Council recommend constant compliance with principles of prudence and alertness while scientific knowledge on the subject increases.

Considering that any medically assisted reproduction using spermatozoa from an HIV-positive man is still insufficiently safe, medical teams already registered with the Health Ministry must not provide such assistance except in the framework of a pluridisciplinary research protocol covered by the law dated December 20th, 1988 and in particular by an opinion expressed by a Consultative Committee for the Protection of Subjects in Biomedical Research (Comité Consultatif de Protection des Personnes - CCPPRB). Furthermore, in view of the specific characteristics of the issue, an opinion formulated by the National Commission on Medicine and Biology of the Reproductive System and Prenatal Diagnosis (Commission Nationale de Médecine et de biologie de la reproduction et du diagnostic prénatal- CNMBR) can also be requested in accordance with Article R. 184-3-12 of Decree n° 95-558 of March 6th, 1995 issued following law n° 94-654 of July 29th, 1994. In this case, the Minister in charge of Public Health tasks the Commission in agreement with this text after having received the opinion of CCPPRB.

Specific rules regarding written consent from couples in which the man is HIV positive, that is consent to treatment with a risk, will be submitted to CNMBR as will the protocols. In addition, information imparted to couples must emphasise recommendations and preventive measures against HIV transmission before, during, and after the medically assisted reproduction procedures. Special medical follow-up will be provided for that purpose.

Any new data which could affect the safety of procedures will be made known immediately and specifically to all concerned (couples, laboratory staff, etc.) and the subject of protocol modification statements to the above Commission.

Laboratories handling semen from HIV-positive men must be provided with facilities and equipment designed to ensure safe procedures and be approved by the Ministry of Health for biological activities associated with medically assisted reproduction.

To protect against any sense of singularity and discrimination, rather than providing special structures for these couples, they should preferably be treated by medical staff already helping other couples to bear child.

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ANNEUSES

ANNEX 1

Viral summary

A reminder of the HIV replication cycle follows. After entering the cell via a membrane receptor (CD4...) viral RNA is retrotranscripted into double-stranded DNA which is integrated as proviral DNA in the cell genome. The next step is production of viral RNA and proteins, followed by maturation and burgeoning of the infectious virus on the cell surface (2).

Increasingly efficient molecular biology tests can quantify the number of copies either of proviral DNA, or of intra- or extra-cellular RNA, or can detect infectious particles by measuring HIV RNA (viral load) (3).

These recent advances must be kept in mind when an analysis is made of publications. Only viral research completed in the last two years should be considered. Research was done on three constituents of semen : seminal fluid, cellular fractions of semen, and spermatozoa
Viral tests can be carried out on seminal fluid and its viral load does not always correlate with the viral load in blood. Recent research in the USA suggests that viral presence in semen and peripheral blood may come from different reservoirs of infection (14). Attempts to detect spermatozoa-integrated proviral DNA have always proved negative. A single study of testicular biopsies of seropositive individuals has evidenced HIV RNA in spermatogonia (6).

Present status of demand, and ongoing procedures for medically assisted reproduction for couples in which the man is HIV-positive.

HIV discordant couples who request medically assisted reproduction are motivated to bear their own children and reject the idea of adoption.

Two different kinds of couples request assistance:

- those for whom absolutely safe pregnancy is the primary consideration view an unrelated donor as a necessity and are willing to be treated on the same footing as couples afflicted by irreversible male infertility,

- those who are less inclined to accept sterility as an obligation imposed by the risk of HIV transmission, who argue on the basis of impending therapeutic progress, and whose outlook on risk evaluation is close to the views of couples who seek genetic counselling and prenatal diagnosis for a genetic rather than an infectious disease.

It is in fact a complex task to evaluate demand, and response must be adjusted specifically depending on clinical and biological data, on risk of progression of disease, on individual response to treatment, and on a psychological assessment of motivation to bear children.

Medically assisted reproduction with the couple's own gametes includes all methods using processed semen which may give rise, depending on results, to either in vivo fertilisation after insemination, or to in vitro fertilisation which may be assisted or not by microinjection (ICSI). Semen processing consists in isolating spermatozoa from the seminal fluid so that they can become active and fertile. This is a laboratory reproduction of the effects of cervical mucus in sexual intercourse during the ovulation phase.

In fact, HIV is located in seminal fluid either in free form or incorporated in leukospermia leukocytes or germ-cells or "round" cells which are also nonmotile and are some of the precursors of spermatozoa during spermatogenesis.

Studies so far have not succeeded in demonstrating the integration of proviral HIV DNA into the spermatozoal genome. The only possibility is passive adhesion of HIV, to the midpiece particularly, of spermatozoa when they are incubated in vitro in the presence of high concentrations of viral particles (7).

Techniques for isolating spermatozoa from the seminal fluid involve separation by centrifugation gradients plus repeated washing and upward migration of the more mobile spermatozoa. Protocols associating all of these techniques manage to eliminate in more than 99% of final preparations the potentially contaminating leukocytes or round cells.

Since semen can be frozen without suppressing fertility before any medically assisted reproduction procedure begins, it is possible to do viral investigation of a specimen of ejaculate which could later be processed. In the last two years, molecular biology has progressed to the extent that it is now possible, inter alia, to quantify viral load in the seminal fluid. Three kinds of research are now possible: HIV RNA for which the detection threshold is about 200 copies of RNA/ml, proviral DNA with a detection threshold of 5 copies/ml, and HIV identification in a cell culture.
Procedural practice is not to process semen in which HIV RNA is found, and to verify the absence of proviral DNA if HIV RNA detection is negative in the seminal fluid (which does seem to have always been the case), or if viral load blood assay results are high. Transmission risk must therefore be evaluated in the light of the detection sensitivities of various investigations of the seminal fluid before any decision is taken as regards use for medically assisted reproduction.

ANNEX 2


Chapter II bis

Medically Assisted Reproduction

Art. L.152-1. - Medically Assisted Reproduction is the name given to clinical and biological procedures allowing in vitro conception, embryo transfer, and artificial insemination, and includes any technique having an equivalent effect which permits reproduction, apart from the natural process.

Art. L. 152-2. - Medically Assisted Reproduction is meant to respond to a couple's parental aspirations.

Its object is to relieve a state of infertility the pathological nature of which has been diagnosed medically. It can also have the object of avoiding transmission to a child of a particularly severe disease.

The man and woman forming the couple must be alive, of child-bearing age, married or able to prove that they have lived together for at least two years and have given prior consent to embryo transfer or insemination.

Art. L. 152-9 - Clinical and biological procedures for Medically Assisted Reproduction, as defined by decree of the Conseil d'Etat, are the responsibility of a named practitioner designated for that function in each institution or laboratory which has been officially approved to carry out these procedures.

Art. L.152-10. - Medically Assisted Reproduction procedures can only be initiated after private interviews have taken place between the couple requesting assistance and members of the pluridisciplinary medical team of the centre, who may enlist the help of social services as set up under section VI of the Code on Families and Social Welfare, if required.

In particular, they must:

1° Establish the motivations of the man and woman in the couple and remind them of lawful opportunities for adoption;

2° Inform them of possibilities of success or failure of Medically Assisted Reproduction procedures, and of hardship involved;

3° Give them a file providing guidance on the following in particular:

a) A summary of legislation and regulations concerning Medically Assisted Reproduction;

b) A description of the techniques;
c) A summary of legislation and regulations concerning adoption, and addresses of associations and organisations who could provide them with further information.

The application can only be confirmed after a period of a month for reflection has expired after the last interview.

Confirmation of the application is made in writing.

Medically Assisted Reproduction procedures must conform to health safety rules as defined by decree of the Conseil d'Etat.

Medically Assisted Reproduction cannot be initiated by the physician when applicants do not meet the conditions prescribed by this chapter or when the physician considers, after consulting with the pluridisciplinary team, that a further period for reflection by the applicants is needed to protect the interests of the future child.

Art. R. 184-3-12 - Each of its sections or the Commission sitting in plenary session, expresses an opinion of matters pertaining to medicine and biology of the reproductive system and prenatal diagnosis which are put to it by the Minister in charge of Public Health.

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