Risk of cytomegalovirus transmission by cryopreserved semen: a study of 635 semen samples from 231 donors

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BACKGROUND: The hypothetical responsibility of sperm donation in cytomegalovirus (CMV) transmission to recipients and precautions to prevent this transmission are widely discussed. The aim of this French CECOS Federation study was to evaluate both the reality and the importance of the CMV risk due to donor sperm and the relevance of measures used to screen it. METHODS: We conducted a prospective multicentric study. CMV was detected by rapid and conventional cultures and by PCR in the frozen sperm of donors who met the normal criteria required of semen donors, irrespective of their CMV serological status. RESULTS: 635 samples from 231 donors (39.4% IgG+) were obtained and tested by culture; 551 samples from 197 donors were also tested by PCR. From those samples, 0.78% were culture+, 1.57% culture+ and/or PCR+; 3.3% of seropositive donors and 0.72% of initially seronegative donors were culture+, but in the latter seroconversion occurred during the quarantine period; of the 197 PCR-tested donors, 3.5% (6.2/1.7) were PCR+, 3.3% (5.3/1.45) culture+ and/or PCR+. PCR+ samples can be culture± and vice versa. The most strongly positive sample corresponded to an initially seronegative donor. CONCLUSION: The best strategy to prevent potential CMV risk is to test donors for CMV IgG and IgM antibody at the outset and after a 6 month period of quarantine and to reject initially IgM seropositive donors or donors who seroconvert during the quarantine period.

Key words: cytomegalovirus/gamete donation/semen/screening of donors

Introduction

Over the last 3 years, 16 teams of the French CECOS Federation have designed a study to evaluate the reality and importance of the cytomegalovirus (CMV) risk due to donor semen and to assess the relevance of measures used to prevent it. This work lies within a dual context: on the one hand the medical and scientific uncertainties on the epidemiology of human CMV infection and, on the other hand, the debates concerning measures to take in order to avoid the potential risk of contamination related to sperm donation.

CMV infection is the most frequent congenital infectious risk: among 10 000 newborns, one to five show obvious clinical signs (Alford et al., 1990; Stagno et al., 1997a) whereas 20 to 250 have asymptomatic viral excretion (Perol et al., 1994) revealing a congenital infection which will cause sensory impairment in a number of these infants.

CMV infects most of the world’s human adult population. At the age of reproduction, 50–95% of all people have CMV antibodies; so, the prevalence of seronegativity among women of this age is thought to be from 0 to 50% depending on the socio-economic background and the origin of the population studied (Perol, 1994)

A CMV primary infection, generally asymptomatic, usually leads to a permanent infection with possible subsequent reactivations causing secondary viral excretion. Reinfection may occur in immune persons because of antigenic and genetic disparity among CMV strains and cause a secondary active infection (Perol, 1994). Co-infection with multiple strains of CMV in semen of homosexual men has been demonstrated

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† Died prior to end of study.
suggesting that reinfecion of the genital tract and probably other sites is relatively common in promiscuous populations. Adult sexual activity is one of the means by which CMV is transmitted, but it is not the only one (Yow et al., 1988; Collier et al., 1990). Oral and respiratory spread appear to be the dominant routes of transmission during childhood and probably adulthood as well. Young infants and children with subclinical infection appear to be a major source of infection in pregnant women.

According to the European Study (Griffiths et al., 1984), ~1–4% of seronegative pregnant women are affected by a primary infection; transplacental contamination occurs in 30–50% of these cases (Stagno et al., 1986). In developed countries, two-thirds of all congenital infections result from a primary infection (Perol, 1994).

Ten percent of maternal primary infections result in symptomatic neonatal disease (Fowler et al., 1992; Mazeron et al., 1994). This disease, often severe, induces 10–30% of neonatal deaths and 50–90% of neurological or neurosensory after-effects (Pass et al., 1980; Fowler et al., 1992; Salzman et al., 1992). On the whole, secondary maternal infections lead to <5% of fetal contamination, mostly subclinical; however, 5–8% of these congenitally infected newborns develop secondary neurosensory impairment, detected during the first years of life (Stagno, 1977b; Fowler et al., 1992). These disorders are thought to be related to evolutive infraclinic encephalitis. Cases of severe pathology in neonates born to mothers who were seropositive before their pregnancy were regarded as exceptional (Ahlfors et al., 1981; Rutter et al., 1985); however, three recent American, Swedish and Belgian studies report that respectively 17, 26 and 40% of symptomatic congenital infections result from initially IgG seropositive (IgG+) mothers (Boppana et al., 1999; Ahlfors et al., 1999; Casteels et al., 1999). The rarity of reinfection compared with reactivation is now put into question.

The detection of CMV in the genital tract and semen has been reported by several groups since 1975; nevertheless, many studies involved selected populations, notably immuno-compromised patients or patients with venereal infections (Lang and Kummer, 1975; McGowan et al., 1983; Spector et al., 1984; Handsfield et al., 1985; Rinaldo et al., 1986; Biggar et al., 1983; Detels et al., 1994).

There are very few data about the incidence of viral detection in the semen of healthy men referred for infertility. Levy and Coll (1997) detected CMV in the sperm of 2.85% (culture) to 8.1% (PCR) of CMV IgG+ men from 100 couples who were candidates for IVF. Previously, two other studies presented different and contradictory results: 0% (culture and hybridization) among 60 men including 30 CMV+ versus 32.7% (PCR) among 217 men from a 92% seropositive population referred for infertility (Bantel-Schaal et al., 1993; Shen et al., 1994).

The only study on cryopreserved donor semen is that of Mansat et al. (1997) of the Toulouse and Montpellier CECOS: on 178 samples from 97 donors including 51 (52.6%) CMV+, the virus was detected in 2.8% of samples with culture or 5.6% with PCR, only among seropositive donors, that is to say 4.5 or 8.1% of these CMV+ donors.

As a result of questions concerning the possible responsibility of gamete donation in the CMV contamination of the recipient, a series of guidelines or legal clauses has been created: the American Fertility Society (1990; 1993), the British Andrology Society (BAS) (Barratt et al., 1993) advise the use of gametes from seropositive donors only for seropositive recipients. In 1994, French Law went a step further and required checking for donor negativity for biological CMV markers; however, in 1996 it went back to clauses similar to American and English recommendations for the matching of serologies accompanied by a quarantine, as in American guidelines. If the test is repeated after quarantine this would allow identification of seroconversion of initially seronegative donors (French Law, 1994; 1996). In 1999, the new BAS guidelines recommended the refusal of seropositive donors; resulting in considerable debate on the justification and the consequences of that measure (Curson and Karadosta, 2000; McLaughlin, 2000; Liesnard et al., 2001).

Within this context, the study of the CECOS Federation aims to: (i) determine the frequency of sperm donors carrying the CMV, so as to be able to evaluate the potential risk of transmission by gamete donation; (ii) assess the permanence or intermittence of the excretion; (iii) determine with what fraction of sperm infectivity is associated; (iv) specify the predictive value of serological data concerning the risk of contamination by donation; (v) try to assess the diagnostic performances of the virological techniques implemented; (vi) suggest an opinion on the relevance of screening standards currently used in semen donation practices, and, if necessary, propose a more suitable recommendation.

Materials and methods

Semen donors

Semen donors were recruited from 16 sites in France. Only potential donors who met all the criteria required to be accepted as semen donors, independent of the CMV serological criteria, could be included in the study: healthy, voluntary donors, aged <45 years, with no family history compatible with a potentially serious heredity risk, belonging to a stable heterosexual couple, with at least one child and whose cytological and bacteriological semen characteristics range within required quality and safety standards; serological tests for HIV 1 and 2, HTLV 1 and 2, hepatitis B and C, syphilis, must all be negative. The donors agreed to participate by signing an informed consent form and the protocol was approved by the institutional ethics committee.

Anti-CMV antibody testing

Serum samples for detection of anti-CMV immunoglobulin IgM and IgG antibodies were collected at the onset of the study and 6 months later. Serological tests were performed using enzyme immunoassays Eti-Cytok-G Plus and Eti-Cytok-M plus from Diasorin (Antony, France) for detection of IgG and IgM respectively.

Semen samples

Ejaculates were processed according to a standardized procedure (Sherman, 1977). The specimens were incubated for 30 min at 37°C and then diluted 1:1 in cryoprotective medium (Ackerman medium). The mixtures were divided into 200 μl straws and frozen in liquid nitrogen. Three ejaculates per donor were assayed for the presence of
CMV: the first and the last and at least one other at random. Two 200 ml straws per ejaculate were thawed and mixed. A 100 ml aliquot was immediately diluted 1:10 in Eagle’s minimum essential medium and was used for culture assays. Three 100 ml aliquots were immediately frozen at -80°C and kept for DNA detection. For the ejaculates that tested positive by culture or PCR assay, if possible two other straws of the same ejaculates were thawed, mixed, diluted 1:1 in phosphate-buffered saline and submitted to centrifugation at 700 g for 10 min. Supernatant and cell pellet were then submitted to cell culture and PCR assay. In addition, the possible other ejaculates from this donor were submitted to cell culture and PCR assay as described below.

CMV detection
Rapid culture was done by inoculating 100 μl of diluted samples onto each of three wells of a 24-well plate seeded with human fibroblasts MRC5 (bioMérieux, France). After incubation for 48 h, cell monolayers were stained by the indirect immunoperoxidase technique with monoclonal antibody E13 and marked cells were counted. A control consisting of a known suspension of extracellular virus (reference strain AD169) was included in each series. The results were expressed as the number of infectious centre-forming units (ICFU) per ml of semen. Conventional culture was performed by inoculating 500 μl of each diluted semen sample onto a 25 cm² flask. Passages of the inoculated cells into fresh fibroblast monolayers were performed after 2 weeks and incubation was continued for a total period of 4 weeks or to the appearance of a CMV-induced cytopathic effect (CPE). CMV isolates were kept frozen in liquid nitrogen.

Detection of CMV DNA by PCR
Detection and quantification of CMV DNA were carried out with Cobas Amplicor CMV Monitor® assay (Roche Diagnostic System). The test allows amplification of a 365 bp fragment within the UL54 DNA polymerase gene. Quantification is achieved by incorporation of a quantification standard into each specimen at a known copy number. CMV DNA levels in the samples were determined by comparing the absorbance of the specimen to the absorbance obtained with the quantification standard. The test was performed according to the manufacturer’s instructions except for the DNA extraction step. For this purpose, 100 μl of semen sample were processed with Nuclisens Lysis buffer (Organon Teknika) according to the manufacturer’s instructions. A 50 μl aliquot of the processed specimen was added to the master mix of PCR amplification. Amplification and detection were automatically performed by the Cobas Amplicor System. One positive control and one negative control provided by the manufacturer were processed with each batch of samples. Results of quantification were expressed in DNA copies/ml of semen. The limit of detection of this quantitative assay was 100 copies per ml of semen.

Results
A total of 635 semen samples from 231 donors were tested: three samples per donor (according to the protocol) for 164 donors, four for 12, only two for 40 donors and only one for 15. The CMV serological tests were initially performed by the different recruiting centres, but they were all centralized and confirmed by one team alone, having no knowledge of the initial results: 91 donors were IgG + when first tested at recruitment, two of them were IgG ± and IgM+, one presented a borderline result for IgM serology.

<table>
<thead>
<tr>
<th>Donor no.</th>
<th>Ejaculate no.</th>
<th>Rapid culture</th>
<th>Virus isolation</th>
<th>PCR: genome copy number/ml</th>
<th>Antibody testing</th>
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Analysis of additional samples
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Titres: expressed as infectious centre-forming units (ICFU).
Number of copies: expressed as ml/log10, after correcting dilution factors.
*Serological check >6 months later: IgG+ IgM- (progressive elevation of IgG titre concentration in the three tested sera).

Table I. Semen samples that tested positive by tissue culture and/or PCR assays

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<th>Donor no.</th>
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CMV transmission risks and semen donation

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the four ejaculates tested, two samples, the first and third, were positive.

**CMV detection by PCR**

Overall, 551 samples, including the five culture+ samples, were tested by PCR. Eight samples from six donors were positive: five samples from three donors (nos. 5, 6, 7; Table I) which were culture- and the three culture+ samples from donors 1, 2 and 3. The sample from donor 1 with the strongest positivity also presented the strongest PCR positivity (>200 000 versus 1000–10 000 copies/ml for other positive samples).

The two culture+ samples (samples 01 and 03) from donor 4 were PCR-; these results were verified and confirmed by repeating amplification twice more.

The three tested ejaculates from donor 5 were positive: they were the first, second and fourth of the donation protocol. For donors 6 and 7, only one of the three tested samples was positive: the fourth for donor 6 and the second for donor 7.

**Serological data on culture and/or PCR+ donors**

One donor (no. 7) was IgG- and IgM- initially and after quarantine. Two donors (nos. 5 and 6) were IgG+ IgM- at the two tests. Three donors (nos. 2, 3 and 4) were IgG+ IgM+ at the first test (borderline positivity for no. 3). One donor (no. 1) was initially IgG- IgM- and then IgG+ IgM+ at the end of the quarantine.

**Analysis of additional samples from positive donors**

A fifth sample for donor 4 and a fourth for donor 5 were tested. Sample 03 from donor 5 was culture- PCR+, sample 05 from donor 4 was culture+ PCR-.

**PCR and culture testing of cellular and fluid fractions**

Of the three positive samples from donor 4: in all three cases, the two cellular and fluid fractions were culture+ PCR- with a stronger positivity for the cellular fraction; this analysis was performed only by PCR for the four PCR+ ejaculates from donor 5: one not valid and three negative results for fluid fraction and two positive/two negative for cellular fraction.

**Discussion**

Currently, there is considerable controversy and debate about the CMV-related risk in reproduction and to what extent semen is involved. The likelihood that semen may carry the virus is not disputed: the presence of CMV in semen has been widely reported (Lang and Kummer, 1975; Biggar et al., 1983; McGowan et al., 1983; Spector et al., 1984; Hansfield et al., 1985; Rinaldo et al., 1986; Bantel-Schaal et al., 1993; Detels et al., 1994; Shen et al., 1994; Rasmussen et al., 1995; Levy et al., 1997; Mansat et al., 1997; Witz et al., 1999). There are differences of opinion concerning the frequency and importance of CMV excretion in the semen of healthy adult men, not immunocompromised and free of genital infection (Lang and Kummer, 1975; Bantel-Schaal et al., 1993; Shen et al., 1994; Levy et al., 1997; Mansat et al., 1997; Witz et al., 1999).

Opinions also differ about the criteria capable of identifying the population of concerned men and the measures needed to avoid potential semen-related CMV risk, notably in semen donation (British Andrology Society, 1999; Curson and Karakosta, 2000; McLaughlin, 2000; Liesnard et al., 2001).

The results of our study contribute to answering the above questions. The 231 donors included in this prospective study were recruited by 16 medical teams of the French CECOS Federation all over France. They are representative of the population of donors in France, recruited according to legal criteria currently in force (mean age: 35 years 7 months, 39.4% CMV+). Of the 635 samples tested in culture (mean: 2.75 tested samples/donor), 0.78% (5/635) were positive, equating to 1.73% of all donors (3.3% of initially seropositive donors and 0.72% of initially seronegative donors). Of the 551 PCR-tested samples, 1.45% (8/551) were positive, that is to say 3.5% of all donors (6.2% of initially seropositive donors and 1.7% of initially seronegative donors). On the whole, 1.57% of samples (10/635) were culture+ and/or PCR+ (3.05% of donors, 5.3% of seropositive donors, 1.45% of initially seronegative donors).

These findings have confirmed previous results about the possibility that healthy men may carry CMV in their genital tract and semen. The proportion of donors in which the virus was found in their semen is consistent with those of other studies (Levy et al., 1997; Mansat et al., 1997). The latter is the only study involving a retrospective series of 97 donor semen. The results of these studies differ from others (Shen et al., 1994; Witz et al., 1999), perhaps because the populations studied and methods used were different.

Unlike Levy et al. (1997) and Mansat et al. (1997), who did not find positive samples from seronegative patients, we concluded that 0.7–1.4% of initially seronegative donors produced at least one culture or PCR+ ejaculate. This result agrees with that of Witz et al. (1999), showing numerous PCR+ results in the semen of seronegative men some of whom were seroconverting, while others presented persistent seronegativity for many months. Similar findings have been described for other tissues (Bruggemann, 1993; Larson et al., 1998).

The positive sample of donor 1 who seroconverted, reveals a level of viral excretion 20–100-fold higher than those of positive samples of other donors. The excretion is clearly intermittent: except for donor 5 for whom all four ejaculates tested positive, donor 4 provided only three positive samples out of five, and the others, one out of three. Although our data are not complete, this excretion seems to involve the two fractions of the semen, liquid and cells, with a more pronounced positivity for the cellular fraction (Lang and Kummer, 1975; Rasmussen et al., 1995).

As regards the virological techniques used in our study, there is an excellent correlation between cultures and PCR results for the 541 negative samples of 190 donors. However, concerning the positive samples, only three ejaculates from three donors were culture+ and PCR+, six ejaculates from three other donors were culture- PCR+; and, particularly surprising, three ejaculates from one donor were culture+ PCR-: For one given donor, all the positive ejaculates show the same result.

PCR positivity without infectious viral recovery by culture could be interpreted as better PCR sensitivity but can also question the viability and replication ability of this detected viral material (Liesnard et al., 2001) especially since in these
cases the viral charges assessed by PCR are not lower than those of PCR+ and culture+ samples, as indicated by our data. Similarly, from five positive donors, Mansat et al. had two donors (five samples) culture+ and PCR+ with similar results for two PCR performed in two different laboratories, and three donors (five samples) culture- PCR+. For the latter, the conflicting PCR results from participating laboratories raised questions on the specificity of the amplification techniques used for this particular medium, namely sperm.

Moreover, perhaps the repeated negativity of viral genome amplification of the three semen samples from donor 4 can be explained by the fact that the semen is prepared for cryogeny. In fact, PCR positivity of these samples was later demonstrated by modifying and adapting extraction protocol.

These findings show that molecular methods for detection of infectious CMV in semen still require further development and standardization to be reliable.

In these conditions, what information do serological data provide? Of the seven donors with positive samples, five were IgG seropositive and two IgG seronegative at the first test: three of the IgG positive donors immediately exhibited IgM positivity, one of the two negative donors tested positive in the following months. According to current CECOS practices, four of the seven donations, that is to say 50% of the samples discovered by our study and 100% of those in which the infectious virus was revealed by conventional techniques, would have been detected by serological tests alone; only these four donors out of the 231 tested donors (1.7%) should be rejected.

Other donations (two IgG+ donors and one donor with persistent seronegativity for many months) correspond to five PCR+-only samples whose potential infectivity may not be so clearly demonstrated.

Our results allow us to conclude that the drastic exclusion of CMV+ donors, as has previously been proposed (British Andrology Society, 1999), does not rule out the potential risk related to semen in assisted reproduction treatment, and that it is inaccurate to say ‘this morbidity is completely avoidable by the use of semen from seronegative donors’ (McLaughlin, 2000). Seronegativity is not a guarantee of safety per se: the most potentially infectious donors may be recruited in the population of initially seronegative donors (cf. donor 1); should it be used without a quarantine, the strategy of matching seronegative donors and recipients could be directly opposed to the actual purpose of our research.

To conclude, we consider that, for lack of a specific standardized molecular tool for discriminating semen at high risk of containing replicative virus, the most effective means of preventing potential CMV transmission by sperm donation consists of a strict application of a serological strategy, and in particular IgM, with repeated tests after a 180 day quarantine. This quarantine was, at first, justified by virological risks which, over the past few decades, have created a much greater interest for practitioners in human reproduction than CMV itself, and today, this quarantine is all the more justified for detecting the CMV. We propose maintaining the position adopted over the last few years by the American Society for Reproductive Medicine (1998), the European Society of Human Reproduction and Embryology (Barratt et al., 1998) and by French Law (1996): the only donors who should be excluded are initially IgM+ men or men presenting IgG and/or IgM seroconversion during quarantine.

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