DEBATE

Screening standards in assisted reproductive technologies

Is the British Andrology Society recommendation to recruit cytomegalovirus negative semen donors only, a reasonable one?

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The British Andrology Society recently recommended the exclusion of all cytomegalovirus (CMV) seropositive semen donors to prevent the risk of congenital CMV infection. The recommendation is based on the results of recent studies that identified a high percentage of symptomatic congenital CMV infections in newborns of women with CMV seropositivity pre-existing to pregnancy and on the fact that CMV can be detected in semen of CMV seropositive men. These are not new data. CMV seropositive women can infect their fetuses with their own latent CMV strain that can reactivate, or with an exogeneous strain that can be transmitted to them by a sexual partner, but also by contacts, for example with an excreting child. The efficiency of these various ways of transmission to the fetus and the factors that could influence this transmission are for the moment completely unknown. An infectious virus is recovered by culture in the semen of <5% of CMV seropositive men. Exclusion of a large population of donors on the sole criteria of a positive CMV serology introduces the general message that this part of the male population is also not suitable as possible partners in couples who have no fertility problems. The problem of congenital infection in neonates of CMV seropositive women is a complex one that has just begun to be investigated. No data exists concerning this risk in the setting of assisted reproduction. We think that alternatives to the drastic BAS recommendation exist and should be more deeply discussed.

Keywords: British Andrology Society/congenital infection/cytomegalovirus

Introduction

The correspondence in Human Reproduction (Curson and Karakosta, 2000; McLaughlin, 2000) about the recent recommendation of the British Andrology Society (BAS) to exclude all cytomegalovirus (CMV) positive seropositive semen donors opens a major discussion about risk in reproduction.

Three recent studies attempted to evaluate the natural risk of symptomatic congenital disease and sequelae in newborns of CMV seropositive mothers. Although serological investigations in pregnant women were retrospective and a part of the maternal serological data was not available, respectively 17% of symptomatic congenital CMV infection in a US study (Boppana et al., 1999), 40% in a Belgian study (Casteels et al., 1999), and 26% in a Swedish study (Ahlfors et al., 1999) were attributed to a secondary infection of their mothers (mothers with pre-existing CMV IgG antibodies). Knowing the CMV seroprevalence, the incidence of congenital CMV infection and the percentage of symptomatic congenital infection attributed to secondary maternal infection in these populations, we could estimate the risk of symptomatic congenital CMV infection linked to a secondary CMV infection of the mother at being between 0.45 and 1.25/1000 seropositive woman/pregnancy.

Sources of contamination in CMV seropositive pregnant women: reactivation or reinfection?

What are the sources of contamination in CMV seropositive pregnant women? Which virus is transmitted to the fetus? Are there factors that could influence the transmission? There are no answers to these questions, but elements of reflection in the literature. A study based on a small number of CMV seropositive mothers and their congenitally infected babies has shown that in the majority of cases (six mothers out of seven) the CMV strain repeatedly isolated in the mother was the one that contaminated their babies, even in successive pregnancies (Huang et al., 1980). This is a ‘reactivation’ situation: the mother transmits a CMV strain that had infected her at an unknown moment in her life. This strain has established a latent state or has subsisted in a low replication state from which it reactivates and contaminates the fetus. Studies in CMV seropositive sex partners who excreted CMV have shown that generally the same strain was shed by both partners and that viral shedding was greater among the sex partners of women shedding CMV themselves than among the partners of those who did not shed the virus (Handsfield et al., 1985; Yang et al., 1995). Thus, in a stable relationship, the CMV strain that is transmitted to the fetus is the mother’s, and also the father’s if he is CMV seropositive. The events that induce
the reactivation of the infection and help the virus infect the fetus are unknown. The observation that excretion of the virus seems to be more frequent when the sex partner is also excreting the virus could be due to a continuous exchange of virus (reinfestation) and a kind of chronic infectious state, at least in the genital compartment with a higher and higher quantity of viral shedding. This situation could favour transmission to the fetus. However, shedding of CMV during pregnancy has been demonstrated to be associated with perinatal infection, not with congenital infection (Stagno, 2001). These findings brought up the important question about the route of viral transmission to the fetus in case of reactivation or reinfection. Does the mother need to be viremic or could a local infection (cervical for example) find its way to the fetus? What is the role of humoral and cellular immunity in these congenital infections of seropositive pregnant women? What are the factors that could alter the CMV immunity during pregnancy, as reactivations and excretion of CMV are frequent in immuno-suppressed patients?

What do we know about the risk of reinfection from a seropositive excreting donor?

Co-existence and succession of multiple strains of CMV in the same individual have been shown, but mainly in the setting of sexually transmitted disease (STD) clinic populations or immunodeficient patients such as HIV seropositive patients or organ transplanted patients (Chandler et al., 1987; Grundy et al., 1988; Collier et al., 1989; Leach et al., 1994). In non-monogamous couples, one can imagine that an exogeneous CMV strain (reinfestation) can locally infect at least the pregnant woman, but we do not know if this strain can infect the embryo. Thus even if one considers that being inseminated is comparable to being exposed to CMV by sexual activity with multiple partners, the risk that this infection, if it exists, results in a congenital infection is not evaluated. Another common source of CMV contamination in women of childbearing age is contact with children who are excreting the virus (Pass et al., 1986). This mode of transmission is very frequently responsible for primary infection during pregnancy. But we have no evidence that CMV shed by children could infect CMV seropositive women and that this virus is able to infect the fetus. Thus the transmission of the donor’s strain is just one of the multiple possible sources of CMV infection in CMV seropositive women; other sources will not be prevented by the use of seronegative semen donors.

Evaluation of the risk in assisted reproduction

Finally the scarcity of data on CMV detection in semen of men free of HIV infection either by culture or by molecular techniques such as polymerase chain reaction (PCR) and the lack of standardization of these methods applied to semen is striking. The argument of the BAS is essentially based on the fact that CMV is detected in semen of CMV seropositive donors. But, is the detection of CMV in semen relevant to the problem of congenital CMV infection in CMV seropositive women in artificial insemination by donor (AID)?

Two studies based on CMV cultures show CMV in 0.4% (seroprevalence not detailed) (Tjiam et al., 1987) and in 4.5% of semen samples of CMV seropositive donors (Mansat et al., 1997). Among CMV seropositive men consulting for infertility 2.85% of semen samples were CMV culture positive (Levy et al., 1997). Isolation of CMV in cellular culture is correlated with the infectivity of the virus. These three studies examined ~400 semen samples. Four studies used molecular techniques to detect CMV and explored ~450 semen samples: hybridization did not detect CMV in 30 semen samples of seropositive men (Bantel-Schaal et al., 1993) and three studies used PCR but the results were far from being comparable (2.85, 8.1 and 33% of positive results) for reasons explained partly by the methods and partly by the origin of the studied populations (Yang et al., 1995; Levy et al., 1997; Mansat et al., 1997). The study recovering CMV in 33% of semen was done in an almost 100% CMV seroprevalent Taiwanese population (Yang et al., 1995) and in the study by Mansat et al., discordance in PCR results was observed between participating laboratories. PCR and hybridization detect a very small part of the viral DNA and do not provide any indication on the viability and replication capacity of this DNA. Moreover PCR in the setting of semen investigation needs standardization of protocols and quality control. Many previous experiences with PCR have shown that problems of specificity and sensitivity are frequent and could be implemented by quality control and participation in an evaluation programme (Zaaijer et al., 1993; Noordhoek et al., 1994; Schirm et al., 2000). In the light of all the above mentioned results, it seems very premature to conclude that CMV seropositive semen donors are ‘bombs’ for their receivers since in 95% of their semen samples replicative virus is not recovered and since the frequency of transmission of the virus to the receiver is still unknown.

Is there an alternative to the BAS recommendation?

The precautionary principle would recommend taking ‘all reasonable measures even if the level of the risk is unknown’. Is the BAS measure a reasonable one? On the basis of this measure, in Belgium, we should refuse almost half of our semen donor population (Liesnard et al., 1998) and in Taiwan, nobody is a suitable semen donor because this country has a 100% CMV seroprevalence (Yang et al., 1995). Dr McLaughlin said in her letter that ‘it is not the size of the risk that is important but the fact that simple steps can be taken to reduce this risk’ (McLaughlin, 2000). This is a disputable affirmation. To close down all AID programmes is certainly ‘a simple step that would undoubtedly reduce the risk’ (McLaughlin, 2000). But excluding half the male population from sperm donation implicitly suggests that half the population takes unacceptable risks when having children naturally. This is a bad and wrong message. The extension of this kind of approach to genetic diseases (we all carry four recessive disorders as a mean) will drive us to consider that nobody is a suitable donor for reproduction. This would be the inevitable
conclusion of ‘a run for absolute safety’ in assisted reproduction although the natural reproductive process is a risky one. The general reflection about safety should stop us from seeking the myth of zero risk. In the present stage of our knowledge, we think that a reasonable measure would be to take into account the CMV seroprevalence of the considered population. Very low CMV seropositive rates would lead us to consider it reasonable to exclude CMV positive donors whereas 100% seroprevalence, such as in Taiwan, shows the absurdity of this exclusion. In 1996 members of the BAS took part in a consensus statement on gamete donation guidelines that circulated among a large number of European specialists and was discussed in a special meeting of the ESHRE. The final document recommended not to exclude CMV seropositive donors but to match CMV seronegative donors and receivers (Barrat et al., 1998). Since that discussion, no new fact concerning CMV has appeared that justifies the changing of this recommendation. However we agree that it is urgent to investigate this risk and its consequences more deeply, as we have previously insisted (Liesnard et al., 1998). If a consensus arises that positive CMV donors carry a significant risk, an alternative to rejection of donors may be to develop a sensitive and specific molecular method well adapted to semen and standardized to help accurately detect the virus in CMV seropositive semen. Quantitative criteria using molecular tests can help in discriminating semen donations at a high risk of containing replicative virus. Elimination of a part of the positive donations would in these conditions be a more conservative although safe way of preventing a possible risk of fetal infection and should be discussed as an alternative.

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References


