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REVIEW

Congenital HCMV and assisted reproduction: Why not use the chance for primary screening?

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Abstract HCMV is the leading cause of congenital infection, with 0.5–0.9 % of infants affected in Europe, and primary maternal infection from the preconceptional phase to the first half of pregnancy bears the highest risk for long-term sequelae-like mental retardation, visual impairment, and progressive sensorineural hearing loss. As compared to couples conceiving spontaneously those under infertility treatment are well accessible to primary HCMV prevention. Since they face higher risk pregnancies this chance should be considered. The concept comprises serological screening for HCMV-IgG, including the partner where appropriate, defining individual risk factors, and counselling on hygiene at the initial assessment of infertility treatment. If seroconversion occurs, the subsequent treatment cycles should be postponed by 6 months. Uncertainties of diagnosis in early pregnancy which may lead to precautious elective termination can be prevented. A newborn at risk of congenital HCMV infection can be identified and scheduled for laboratory and paediatric evaluation within the first 2 weeks of life.

Keywords Non-primary HCMV infection · Screening · Hygiene · In vitro fertilisation (IVF) · Primary prevention · Artificial reproductive technologies (ART)

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Introduction

While the incidence of rubella embryopathy has been widely reduced due to systematic vaccination and prenatal screening programmes, Human cytomegalovirus (HCMV) has taken its place as the most prevalent infectious cause of embryo-fetopathy. In Europe, still an estimated 0.5–0.9 % of children are born with congenital HCMV infection, and it has remained the most frequent cause of non-genetic mental retardation and progressive sensorineural hearing loss (SNHL) in early childhood [1–6].

Primary maternal infection clinically implies the most relevant individual risk of vertical transmission. Since it usually goes unnoticed, maternal infection as well as congenital HCMV infection and disease is difficult to recognise, and early pre- and postnatal diagnosis can easily be missed. Because of diagnostic and therapeutic uncertainties, incidental prenatal diagnosis of maternal infection may end in precautious elective termination of pregnancy [7–11], and the benefit of a universal screening programme in pregnancy is yet under debate [12, 13]. An effective vaccine has not been developed to date.

In couples treated for infertility, the issue of ambiguous results in pregnancy leading to invasive procedures like amniocentesis and eventually termination of pregnancy is not desirable and should be avoided whenever possible. Therefore, the advantage of effective primary screening and prevention should be considered: in contrast to the fertile population, the group of patients treated for infertility can easily be addressed before planned conception, and the partner is also available.

In Europe, an increasing proportion of children is born after infertility treatment. In Germany, more than 10,000 per year (1–2 % of all newborns) [14] have been conceived after in vitro fertilisation alone. Bearing in mind that the

resulting pregnancies per se are more often complicated by, e.g. multiple gestation, premature delivery and intrauterine growth retardation than those conceived spontaneously, there are further arguments to discuss why primary screening is worth implementing in this group of parents: children at higher risk for adverse outcomes can be protected from another hazard, and from preconception to the postnatal phase this would require relatively little extra effort.

By reviewing current extensive literature, we intend to provide a basis for risk estimation and to suggest a concept for primary HCMV screening focussed on reproductive medicine.

Epidemiology

Like other members of the Herpesvirus family, Human Cytomegalovirus (HCMV) leads to a latent lifelong infection which only rarely compromises immunocompetent individuals. Being well adapted to its human host, it hardly gives rise to any symptoms when contracted postnatally e.g. after term delivery. It is endemic worldwide, and seroprevalence is known to vary with nationality, age, gender, and socioeconomic factors. Several genetically distinct strains of the virus have evolved, but it is not clear to which extent they can result in secondary infection or induce reactivation [15, 16]. While seroprevalence is close to 100 % in less developed countries, it has declined considerably over the past decades in more industrialised countries [17]. Girls and boys have a similar serostatus in childhood and adolescence (29.9 vs. 30.3 %) [18]. In childbearing age, women more deliberately contract the virus than men, possibly due to occupational or familial factors. Still, about 50 % are seronegative and susceptible to primary HCMV infection [2], and this also applies to women who undergo infertility treatment (Table 1) [19]. In the near future, general HCMV seroprevalence may not decline further, because migration is a constant factor as well as early admission of young children to day care centres.

Clinical and laboratory characteristics of HCMV infection

The primary phase of infection is rarely recognised. After incubation period of 4–6 weeks, unspecific symptoms like fever, night sweats, headache, rash, pharyngitis, malaise, lymphadenopathy, splenomegaly, and hepatitis may occur, but usually are self-limiting within 2–4 weeks [10]. After replication in various tissues, the virus is excreted in breast milk and urine, less consistently in saliva, tears, and genital secretions for at least 6 months. After 3–8 weeks neutralising CMV IgG antibodies develop and reach their maximum titre after 4 months [20]. Although difficult to assess, infectivity may be highest during this time in healthy adults. In blood, the viremic phase is difficult to diagnose because the virus has a high affinity to mononuclear cells [21]. HCMV DNA detected in plasma serves as a surrogate marker for viremia, and detection coincides with the beginning of HCMV antibodies formation [22].

During the latent phase, the virus is harboured mainly in hematopoietic stem cells and macrophages, and an immunocompetent host can shed the virus periodically at low levels for lifetime without showing symptoms.

Individuals under immunosuppression, namely patients suffering from AIDS, transplant recipients of solid organs and human stem cells are threatened by primary infection and reactivation of the latent virus.

The serostatus can sufficiently be evaluated outside the context of pregnancy by testing for HCMV-IgG. Diagnostic problems occur when primary infection needs to be differentiated from non-primary infection in pregnancy, and when the foetus needs to be evaluated on the basis of an uncertain maternal serostatus. Further serological tests are recommended, but DNA detection in maternal blood or plasma is not conclusive. Laboratory diagnostic tools and therapeutic issues in pregnancy are reviewed elsewhere (e.g. [1, 2, 23]), and should be applied under the advice of a specialised laboratory.

Characteristics of congenital HCMV infection

Primary infection of a seronegative mother overall implies a 30–40 % risk of vertical transmission. Viral transmission rates apparently rise with gestational age, e.g. from 5 to 10 % when the mother seroconverts in the preconceptional phase, up to 35 % in the first half of pregnancy and 80 % in the third trimester. Conversely the unborn is more likely to develop severe symptoms when it gets infected before the 20th gestational week. Severe sensorineural impairment most likely resembles teratogenic effects in the embryonic and early foetal phase of development, but a systematic evaluation on this issue is not available.

Several observational studies deal with transmission rates in the peri- and preconceptional phases of pregnancy, setting out from diagnosis in early pregnancy. Unfortunately, the definition of the phases is inconsistent, and the exact time of primary maternal infection can neither be recalled nor assessed by laboratory criteria retrospectively. Therefore, it is difficult to define the safety distance before pregnancy. While Feldman did not detect any cases among 97 women who contracted HCMV prior to 8 weeks before conception [8], according to other authors congenital

Table 1 HCMV seroprevalence in couples under infertility treatment

References	Country	Enrollment	Nulliparous women	Seronegative women	Seronegative men	Concordantly seropositive	Concordantly seronegative	Woman seronegative male partner positive	Woman positive partner negative
Francisse et al. [19]	Belgium	1990–2006 2463 couples (100 %)	76.5 %	46 % of 3,227	57 % of 2,565	32 %	36 %	9 %	22 %
Kling and Kabelitz [49]	Germany	2002 727 couples (100 %)	100 %	55 % of 742	67 % of 817	21 %	42 %	13 %	25 %

infection cannot be excluded with safety when primary maternal disease occurs within the previous 12–18 weeks [7, 24]. Within 8 weeks prior to conception until the second gestational week 4.6–8.8 % is affected [8–10]. One study reported on four affected in 24 pregnancies (16.7 %); one of these ended in first trimester termination and three in delivery of asymptomatic newborns [7].

From the paediatric point of view, congenital HCMV infection causes connatal symptomatic disease in about 11 % of infected newborns [3, 4], but it can also result in neurological sequelae which may not be obvious at birth. Perinatal death occurs in nearly 5 % of infected children, and symptoms in the newborn period comprise jaundice, petechiae, hepatosplenomegaly, microcephaly, retinitis and optical atrophy as well as seizures. When symptomatic at birth, their risk to develop permanent disability is high. An estimated 50 % may suffer from mental retardation and/or sensorineural hearing loss (SNHL). Visual impairment is reported to occur in 22–58 % [2–5]. For children who were born asymptomatically the risk to develop sequelae is 10–15 % [5, 25]. Audiometric testing may reveal progressive hearing impairment within the first 2 years and beyond in about 10 % [25]. The prevalence for these deficits in the general population is considerably lower. Childhood hearing loss occurs in 0.4 %, developmental delay in about 4.5 % of preschool children, and major or minor behavioural disorders of any cause are diagnosed in about 12 % of children below 10 years of age [26].

Postnatal HCMV infection can cause life-threatening septicaemia in prematurely born infants but does not lead to long-term sequelae comparable to congenital infection [27]. Therefore, early diagnosis of congenital HCMV infection is warranted. Within 2 weeks after birth, differentiation is possible by laboratory testing of blood, saliva or urine specimens; but later on, postnatal infection, e.g. via breast milk cannot be excluded. Diagnosis should be ascertained by a specialised or reference laboratory.

Community-acquired HCMV infection

For natural infection, recurrent intimate physical contact is necessary. Apart from congenital infection, the most contagious reservoir of the virus is breast-feeding seropositive mothers who undergo reactivation of the virus in about 35 % [28], and infants and toddlers under 3 years of age who can shed the virus for years. Urine seems to be the most contagious body fluid [29].

Moreover, unprotected sexual intercourse with seropositive partners can lead to seroconversion in young adults. Several studies suggest that promiscuity plays an important role in this process, and protected intercourse

was found to reduce the rate of transmission in young women attending a department for sexually transmitted diseases (STD) [30, 31]. The most contagious partners may be those who undergo primary infection themselves [19].

In industrialised countries, the overall annual and pregnancy seroconversion rate is as low as 0.5 % [2, 32]. In the 1990s, an annual rate of 0.55 % in a cohort of 24,260 blood donors at the age of 20–60 years, and 1.33 % per year at age 30–35 years was described in German cohorts [33]. The incidence of primary HCMV infection was reported to be less than 0.1 % (14 in 17,982 blood donors) in 2010 [34]. With a donation frequency of four times per year this corresponds to the described annual seroconversion rate.

To our knowledge, there is one study which is concerned with HCMV prevalence in reproductive medicine. A large cohort comprising 3,329 women and 2,665 men who attended a Belgian fertility clinic between 1990 and 2006 could be followed up in a longitudinal study. Similar to our results, they found that most couples had a concordant serostatus, and the group of seronegative women living in a discordant partnership comprised a relatively small group of 8 % (Table 1). Within a period of approximately 2 years of observation, the annual rate of seroconversion was one-tenth of the rate observed among blood donors (0.035 % in men and 0.04 % in women). The risk of seroconversion for seronegative women was not only significantly associated with caring for young children (relative risk 2.65), but also elevated by 6.6 when the partner contracted a primary HCMV infection simultaneously and by 1.7 when living with a seropositive partner. Consequently, they proposed safer sex methods to protect seronegative women who live with a seropositive partner not only in pregnancy but also in the preconceptional phase [19].

This view needs further comment. Since most infertile couples retain a chance to conceive spontaneously, such a proposal will lead to a conflict of interests, and to our knowledge its efficacy in preventing HCMV transmission during a reactivated latent infection within a stable partnership has not been examined. Seminal HCMV contamination is well described, and in Europe, about 6 % of healthy men excrete viral DNA [35]. Since it does not resemble viral infectivity, the clinical significance of this finding in reproductive medicine has been discussed controversely [36]. Seminal fluid does not seem to be a relevant route of transmission [37]. During primary or latent HCMV infection, the virus is probably transmitted on various routes in parallel. Since their annual seroconversion rates apparently are below 0.1 %, we propose to regard this group of discordant couples at low risk for congenital HCMV infection.

Transfusion transmitted HCMV (TT-HCMV)

TT-HCMV is an iatrogenic source of infection, which can be relevant to reproductive medicine. Cellular blood products are considered safe 1 year after primary infection of the donor. Universal leukocyte reduction (less than 1 Mio leukocytes per unit) has been introduced into the standards for preparation of cellular blood components (packed erythrocytes, thrombocytes) in several Western European countries and Canada in 2001. For these products, the risk of transmitting HCMV is estimated 0.1–0.01 % per donated unit, depending on the seroprevalence in the donor and recipient population, and rendered negligible for immunocompetent recipients [38, 39]. Where leukoreduction is not practised, HCMV seronegative blood donors should be preferred for pregnant seronegative women; seronegative women treated for infertility may need the selection accordingly.

Occupational risks of HCMV infection

People involved in the physical care of infants and small children under 3 years of age have been identified as a special risk group for primary HCMV infection. Occupational risks have been found among day care professionals; their risk to contract an infection within 1 year was elevated by the factors 1.8–3.8 [40] and has even been reported to exceed 10 % [41]. The risk of midwives to acquire HCMV infection has not been defined to date. In a prospective controlled study, seroprevalence and seroconversion rates were not elevated in transplant and hemodialysis nurses, neonatal intensive care nurses, and student nurses, as compared to 251 blood donors [42]. In contrast, Sobaszek and co-authors reported on increased risks in health care workers who provide basic care for small children [43] and for adult immunosuppressed patients [44]. In their multivariate analysis, data were unfortunately not adjusted for the probands' country of origin. No association was found among personnel working with mentally disabled children [45]. An important factor to prevent HCMV infection is the level of hygiene, which is more difficult to standardise with mobile children in day care institutions or at home than in hospital. Nevertheless, hygiene instructions have been promoted, e.g. by the US Centres for Disease Control (CDC) not only for prevention of occupational risks, but also for household contacts [46]. Accordingly, in Germany the law for maternal protection in pregnancy ("Mutterschutzgesetz") demands HCMV screening before pregnancy, education on hygienic preventive measures, and an employment ban in pregnancy for women of childbearing age who work in day care units. Important component of protection is frequent use of water and soap and wearing gloves, e.g. when changing diapers.

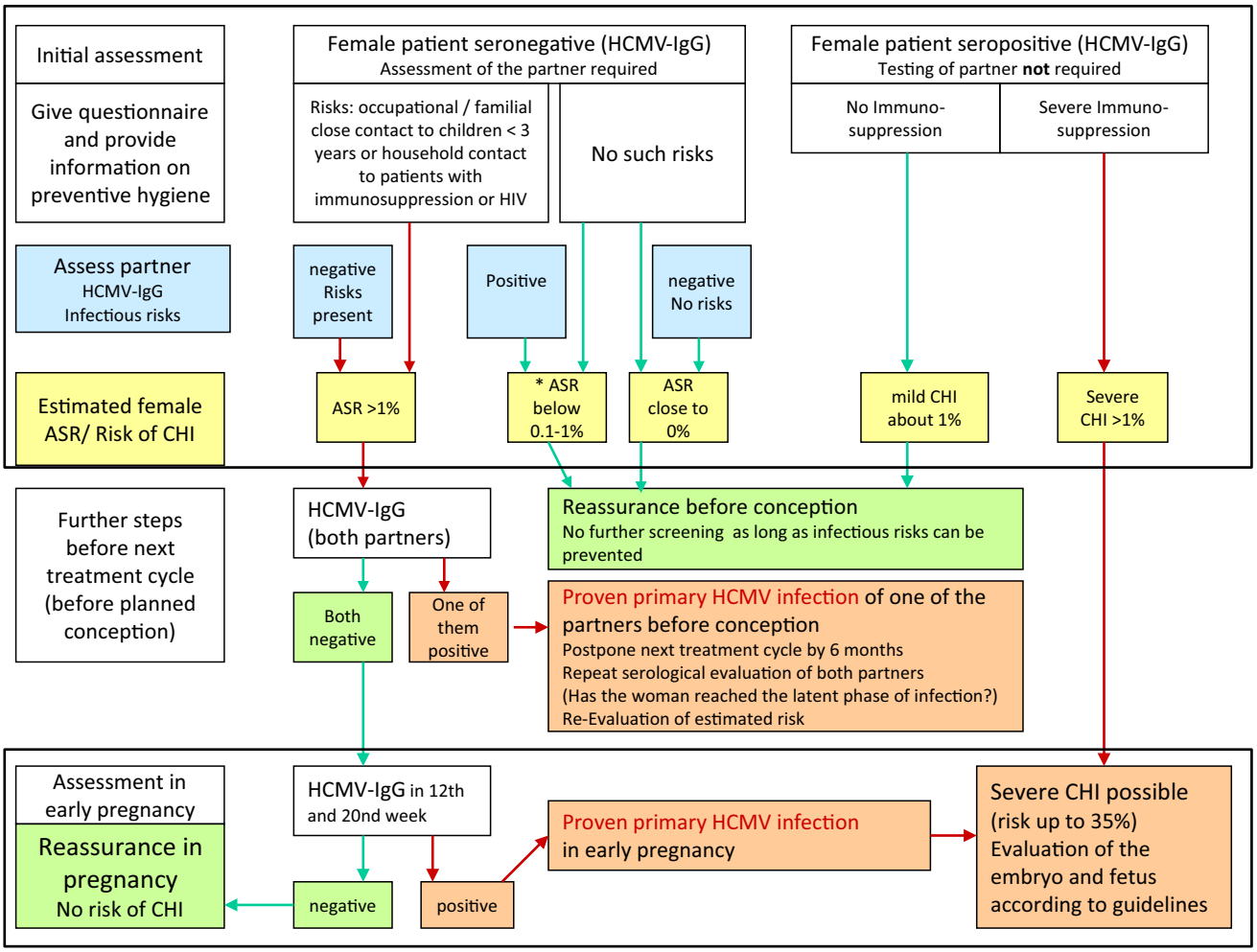

Fig. 1 Proposal for primary prevention of congenital HCMV infection in couples treated for infertility in three steps: at initial assessment, both partners are evaluated by serological testing and a questionnaire, and receive a handout on hygienic instructions. *Green arrows* indicate the diagnostic workup for women at low risk (0–1 %). *Red arrows* indicate the course in case the initial assessment suggests a "high" risk (>1 %). Prior to each treatment cycle, seronegative women/couples at "high risk" (ASR > 1 %) should undergo HCMV-IgG testing. *Asterisk*: Whether the infectious risk of seronegative women who live with a seropositive partner justifies repeated testing is debatable (see text). *ASR* annual seroconversion rate, *CHI* congenital HCMV infection, *na* not applicable

Non-primary maternal HCMV infection

Seropositive women usually are not perceived to be at risk, and diagnostic consequences are not considered in pregnancy [7, 47]. Nevertheless, vertical transmission is also possible. In Europe, an estimated 1 % of children born to seropositive mothers are connatally infected [1–5]. The children are partly protected from severe disease, and as their main problem sensorineural hearing impairment can evolve. On the global level, incidence of congenital infection parallels maternal seroprevalence and exceeds 1.5 % in some parts of the world. Moreover, HIV coinfected mothers have a threefold risk of delivery from an infected infant, which is three to fourfold more likely to be symptomatic at birth and to develop neurological sequelae [2, 4, 48]. Thus, the actual risk of congenital infection depends on the chances for reactivation and secondary infection with a different HCMV strain, that is, maternal immune defense and the circulation of different HCMV strains.

Proposal for prevention of congenital HCMV infection in infertility treatment

Since couples planning infertility treatment are evaluated concerning various parameters, there is a chance to introduce efficacious primary preventive care for HCMV (Fig. 1). It consists of serological HCMV-IgG testing and a questionnaire on familial or occupational HCMV infective risks during the first evaluation. These include close and repeated contact to children under 3 years, own children

attending a day care centre, child minding at home or household contact to a person under severe immunosuppression. To prevent circulation of HCMV all women and their partners should be counselled on hygienic prophylaxis [46]. Nulliparous seronegative women may get along well avoiding close contact to small children, whereas women who have given birth are at a higher chance to be seropositive at initial assessment. Seronegative women need to have their partners assessed as well.

Initial assessment is completed by a risk estimation, which is based on the annual seroconversion rate (ASR) for seronegative women. According to the literature, the mean estimated ASR in European countries is 0.5 % and as low as 0.04 % in couples under infertility treatment [2, 23, 33]. For seropositive women, the risk of congenital HCMV infection (CHI) applies.

Since about 45–55 % of the women will be seropositive, and only a part of seronegative infertile couples will have infectious risks; we assume that the majority of couples can be reassured at this stage. Depending on their individual risk factors, these groups may not need follow-up in the course of their treatment or in pregnancy.

Hygiene instructions are most important to be followed by those individuals who are seronegative and indicate infectious risks, and subsequent testing prior to each treatment cycle and in early pregnancy will be the consequence. In case the female patient shows seroconversion after her initial assessment, the next treatment cycle should be postponed by 6 months. Elaborate serological testing for HCMV IgM antibodies, neutralising IgG antibodies, and avidity may be necessary to rule out whether she has reached the latent phase of infection. In presumably very rare instances when her partner undergoes seroconversion in the preconceptional period, the couple may have to wait for longer before starting again to minimise the risk of congenital HCMV infection.

If infectious risks actually can be avoided due to higher awareness of both partners, maternal HCMV-IgG testing may be sufficient in the 12th and 20th gestational week [47]. Alternatively, monthly IgG testing until the 20th week and foetal ultrasound in the 20th to 22nd week have been proposed recently [2].

At highest risk may be single cases of seropositive women under severe immunosuppression, e.g. compromised immune system due to chronic diseases which either lead to impairment of the immune defense (HIV) or require pharmacological immunosuppression (e.g. after solid organ transplantation, treatment for autoimmune diseases). For them, embryonic and foetal screening is the most important issue.

Our concept is focussed on counselling of couples under infertility treatment and selection of women who actually benefit from follow-up during planned conception cycles and in pregnancy. The issue of an initial assessment can be adapted to couples who do not suffer from infertility but seek medical advice before family planning. The concept can help to identify newborns at risk of congenital HCMV infection. These children will require laboratory and paediatric evaluation within their first 2 weeks of life as well as preventive checkups with an emphasis on audiometric testing until preschool age to support them as best as possible.

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Conflict of interest None to declare.

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