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Does hygiene counseling have an impact on the rate of CMV primary infection during pregnancy? Results of a 3-year prospective study in a French hospital

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ABSTRACT

Background: Cytomegalovirus (CMV) is the most frequent cause of congenital viral infection in developed countries.
Objectives: The objective of this study was to evaluate the impact of our prenatal CMV infection screening and counseling policy.
Study design: Since 2005, all pregnant women in our obstetric center have been informed about CMV infection, and if they agree, given a serological test at around 12 weeks of gestation (WG). If this first test is negative, the women and their partners are given hygiene counseling on how to prevent CMV infection, and a second test is performed at around 36 WG.
Results: Among the 5312 women who had an unknown immune status, or were known to be seronegative when they had their first visit to our center for their current pregnancy, 97.4% agreed to CMV screening. Primary infection was detected in 11 women between 0 and 12 WG (0.42%), and seroconversion was diagnosed in five women between 12 and 36 WG (0.19%).
Conclusions: These results suggest that if clear information is given on CMV infection during pregnancy, the rate of seroconversion is lower following counseling than before counseling.

1. Background

Cytomegalovirus (CMV) is the most frequent cause of congenital viral infection, with an incidence of 0.5–1.0% of all live births in developed countries, and is the leading infectious cause of hearing loss and developmental delay.[1,2] It is estimated that 5–10% of infected newborns are symptomatic at birth, and that among asymptomatic newborns 10–15% will eventually show some developmental disorder(s), mainly sensorineural hearing loss.[1] Although primary maternal infection seems to carry a higher risk for transmission and leads to greater severity of fetal infection, congenital infection and disability can also occur following secondary maternal infection (reactivation of infection or reinfection).[3–7]

In France, primary CMV infection during pregnancy is quite frequent (estimated 0.6–1.4%[8,9]), and whether or not pregnant women should routinely be tested for CMV has been debated. Currently, systematic screening for CMV infection is not recommended in our country, mainly because: (1) neither maternal treatment nor counseling programs have yet proved to be effective, (2) epidemiological data are incomplete, particularly concerning the rate of secondary maternal infection and its consequences, (3) establishing the prognosis of congenital infection is difficult, and (4) it has been thought that the possible adverse effects of screening (anxiety, early elective abortion, abusive use of amniocentesis, etc.) could be more frequent than disorders related to congenital CMV infection.[10] However, this same report also recommends that pregnant women should be given hygiene information.[10] As in other countries,[11,12] and despite its frequency, our experience is that few women have heard of CMV infection, and even fewer are aware of how it can be prevented. Because of the high number of neonates infected, and the public health burden of congenital CMV disease, the development of prevention programs for CMV infection is encouraged by the

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US Centers for Disease Control and Prevention, and the American College of Obstetricians and Gynecologists.[13–15]

2. Objectives

Vaccines are currently under development, and antiviral treatment (using valaciclovir) or passive immunization (using CMV hyperimmune globulin) for pregnant women with primary CMV infection are about to be evaluated in randomized trials.[16–18] However, the modes of CMV transmission to pregnant women are well known, and preventing transmission through behavioral changes could be, at the moment, the most effective and inexpensive way to decrease the risk of CMV infection during pregnancy. This has been shown in prevention programs tested in small groups at high risk of acquiring CMV infection.[19–21] To examine prevention strategies further, we undertook a prospective study designed to assess the impact of a counseling program aimed at modifying potentially risky parental behavior on the rate of maternal CMV infection among a large population of pregnant women. We report here the results collected during the first 3 years of this observation, adding to our previously published preliminary data.[22]

3. Study design

In our obstetric department, the medical staff are accustomed to informing patients about CMV infection, and screening has been offered for many years. The analysis of this epidemiological cohort was undertaken in order to evaluate the impact of our counseling program. Medical data were stored anonymously and protected according to the recommendations of the CNIL (Commission Nationale Informatique et Liberté, authorization numbers 1181076 and 444971).

We retrospectively analyzed the data of all patients who had their first medical visit to our obstetric department between 01 January 2005 and 31 December 2007, and who had been followed until the end of their pregnancy. During their first medical visit to our institution [at 12.4 ± 0.8 weeks of gestation (WG)], each pregnant woman was informed of the possible consequences of CMV primary infection, and the reasons why systematic screening is not currently recommended in France.[10] If patients agreed to CMV screening, serological testing was performed after written informed consent was obtained. If the first CMV serological test was negative [absence of CMV-specific IgG (CMV-G) and CMV-specific IgM (CMV-M)], detailed hygiene information was given to the mother and father both in writing (standard script) and orally, and a second test was performed at 35.6 ± 1.5 WG.

Protective measures relied on frequent hand washing, especially after exposure to a child's saliva or urine (e.g., diaper changes, handling dirty laundry, touching the child's toys, etc.), but wearing protective gloves was not recommended in our institution. It was also recommended to avoid intimate contact with young children (e.g., kissing on the mouth, sleeping together, sharing washcloths, utensils, food or drink, etc.). The counseling was provided by obstetricians or midwives at the first general visit, and lasted about 5–10 min. Patients were free to ask as many questions as they needed during the first visit and during the following monthly visits, and were given a telephone number to call to obtain any additional information.

Except for patients with primary infection, or seroconversion diagnosed during pregnancy, all women had standard management of pregnancy, including three routine ultrasound examinations at 12, 22 and 32 WG. If primary infection was detected, or if seroconversion occurred, fetal ultrasound examination was performed monthly and amniocentesis was discussed. In the case of infections diagnosed at 36 WG, only an ultrasound examination was performed, including transvaginal evaluation of the fetal brain.

CMV-G, CMV-M and CMV-G avidity assays were performed with commercially available assays (LIAISON®, DiaSorin, Saluggia, Italy). According to the manufacturer's recommendations, cut-off values for the avidity index were defined as follows: low avidity index <0.20; moderate avidity index ≥0.20 to <0.30; high avidity index ≥0.30. When the CMV-G avidity index was low or moderate, it was controlled with an in-house test using 6 M urea as denaturing agent, derived from a method previously described.[23] Cut-off values were defined as follows: low avidity index <50%; moderate avidity index ≥50% to <70%; high avidity index ≥70%.

The diagnosis of primary infection was based on the detection of CMV-G and CMV-M, and a low CMV-G avidity index. If the first serological test indicated preconceptional CMV infection [positive CMV-G/negative CMV-M, or positive CMV-G/positive CMV-M/high CMV-G avidity index, or positive CMV-G/positive CMV-M/moderate CMV-G avidity index (identified as preconceptional infection with additional analysis of previous or further samples)], women were told they were immunized, and had no specific follow-up concerning CMV infection, except in cases of fetal abnormalities on ultrasound examination.

Seroconversion was defined as the absence of both CMV-G and CMV-M at 12 WG and the presence of CMV-G at 36 WG. When CMV seroconversion was observed at 36 WG, it was possible to date the primary infection by performing CMV serology on stored serum samples collected for monthly toxoplasmosis testing (mandatory in France for seronegative women). When maternal infection was confirmed, a diagnosis of CMV congenital infection was made in their newborns by urine culture within the 3 days following birth.

Statistical analysis was performed using Stata 8.2 software (Stata Corp., College Station, TX, USA). Crude infection rate data consisted of the number of cases of CMV infection and person-time units for pregnant women who had received hygiene information (12–36 WG), and those who had not yet received hygiene information (first 12 WG). The statistical significance of the incidence risk ratio was evaluated by an exact test based on the Poisson distribution.

4. Results

Among the 5312 women followed in our obstetric department who had an unknown immune status, or were known to be seronegative when they had their first visit to our center for their current pregnancy, 5173 (97.4%) agreed to undergo screening (Fig. 1). Out of the 5173 women tested, 2590 were CMV-G positive (50.1%) and 2583 CMV-G negative (49.9%). We did not observe any major adverse effect of the screening/counseling program, such as alarm or early termination of pregnancy, for any of these women.

Among the 2590 CMV-G positive patients, 141 were CMV-M positive (5.4%). Within the first 12 WG, only 11 out of the 141 CMV-M positive patients had low CMV-G avidity index (7.8%), confirming primary infection; 112 had a high CMV-G avidity index (79.4%), excluding primary infection; and 18 an intermediate CMV-G avidity index (12.8%). These 18 women had further investigations performed using serum collected for HCG evaluation at the beginning of pregnancy, or for monthly toxoplasmosis testing. For 16 of them, infection occurred before pregnancy, for one it was not possible to determine when infection occurred, and for one there were no data because she was lost to follow-up after 12 WG.

If we consider that the 11 patients with primary infection (low CMV-G avidity index) had a negative serology at 0 WG, the number of women who had not encountered CMV by the beginning of pregnancy is the number of seronegative women at 12 WG (2583) plus 11, that is to say 2594, or plus 12 (if we take into account the woman with an undetermined date of primary infection), which

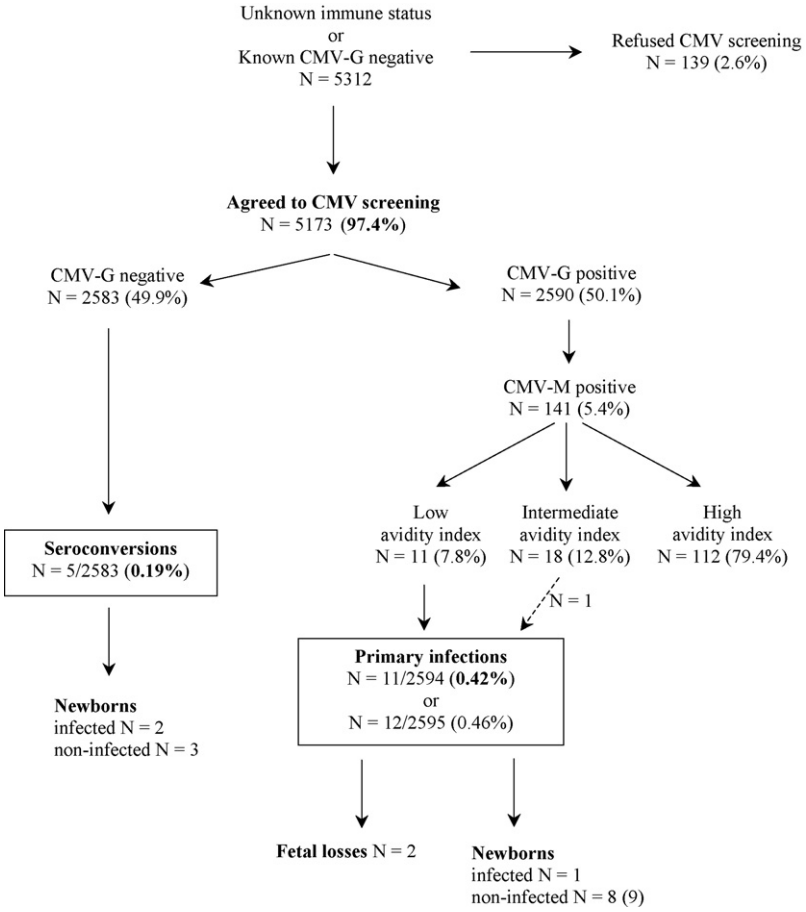

Fig. 1. Overall CMV serological results of the 5312 pregnant women included in the study, and the outcome of pregnancy of those who demonstrated CMV primary infection or seroconversion.

gives 2595. The rate of CMV infection during the first 12 WG was therefore 0.42% (11/2594) or 0.46% (12/2595). For the main analysis, the woman with an undetermined date of primary infection was not taken into account as this did not significantly change the results.

Only five of the 2583 patients who were CMV-G-negative at around 12 WG demonstrated seroconversion between 12 and 36 WG (Fig. 1), giving a rate of CMV infection between 12 and 36 WG of 0.19% (5/2583). Of the 16 cases of maternal CMV infection, 15 occurred in high risk women: nurses in pediatric or childcare centers ($N = 5$), medical doctors ($N = 2$) or women with a child under 3 years of age at home ($N = 12$).

Among the 16 pregnant women who demonstrated CMV infection, there were two spontaneous fetal losses: one at 12 WG and the other at 18 WG. There was no histological proof of CMV infection in either of the fetuses. For the 14 other women, ultrasound examinations performed monthly after the diagnosis of CMV infection were normal until delivery. Amniocentesis was discussed with all CMV-positive women, but only performed in three cases. Eleven babies were born uninfected; of the three born infected, two were to women who seroconverted and one was to a woman with primary infection detected before 12 WG. The child born to the latter woman had petechiae at birth and unilateral hearing loss at 1-year of age. The two other infected newborns were asymptomatic at birth. None of the three children developed psychomotor delay during the follow-up period (24, 33 and 39 months). Furthermore, no abnormality related to fetal CMV infection was observed on ultrasound examination of any of the fetuses of the 5312 pregnant women included in this study.

In total, among the 5173 women screened over the 3-year period, 11 had confirmed primary infection that occurred within the first 12 WG. Among the 2583 seronegative women at 12 WG, five were found to be seropositive at 36 WG. Retrospective analysis of stored serum samples showed that the seroconversions occurred equally during the second and third trimesters of pregnancy, at 18, 20, 24, 27 and 31 WG, respectively. According to these data, the infection rate between 12 and 36 WG was 0.008% per pregnant woman-week, and was significantly lower than the infection rate before 12 WG, which was 0.035% per pregnant woman-week (mid $P = 0.005$).

5. Discussion

All the pregnant women in our cohort were informed about CMV infection and given hygiene information. A randomized trial would not have been ethically acceptable, as current evidence already points towards the probability that behavioral intervention has a benefit, and also considering French recommendations.[10,19–21] During the first 12 WG, before the first visit to our obstetric department, and before hygiene counseling, confirmed primary infection had occurred in 11 women. During the following 24 WG, only five women demonstrated seroconversion. Without any hygiene information on how to prevent CMV infection, we would have expected the same quarterly incidence of seroconversion during the following 24 WG, that is to say twice as many seroconversions between 12 and 36 WG as in the first 12 WG.

The lower incidence of CMV infection after 12 WG could partly result from other factors leading to a lower exposure to

the virus during the second and third trimesters of pregnancy. French women usually stop professional activities between 34 and 36 WG, but the last CMV test was performed at 36 WG so this factor may not represent a bias in our analysis. Lower exposure could also result from reduced sexual risk, which is unlikely, since women probably experience few changes in partner over the 9-month span of a pregnancy. Changes in exposure to young children could also be possible, but are unlikely because women usually stay close to their own children throughout pregnancy. Finally, even if too few seroconversions were observed in our study to give a definitive constant primary infection rate during the 12–36 WG period, the five primary infections diagnosed after hygiene counseling occurred equally during the second and third trimesters.

The rate of seroconversion following counseling was very low (0.19%) compared with the rate in previously published series (0.9–1.4%) in which CMV seroprevalence was similar to ours (51.5–53.9%).[8,24–26] We noticed that among the 16 women in whom CMV infection was diagnosed during pregnancy, 15 were at high risk of acquiring CMV (especially the 12 women who had a previous child under 3 years old at home). It is likely that young children are the main source of maternal infection,[27,28] and hence hygiene information given to the parents is mostly related to handling young children.

The first evaluation of the impact of hygiene information on the rate of maternal infection was performed in small populations at high risk of contamination.[19,20] These studies concluded that counseling may be highly effective for preventing CMV infection in seronegative women who already know they are pregnant. Our results are from a population-based study, the protective behavior recommended was less strict (protective gloves were not recommended), and no monitoring was undertaken to assess adherence to recommended preventive behaviors. However, our results confirm previous studies, and moreover suggest that simple information on basic hygiene measures given to a large population of pregnant women at the beginning of pregnancy could significantly reduce the incidence of maternal CMV infection during pregnancy, and therefore the number of infected fetuses.

The usefulness of serological testing for CMV during pregnancy has been questioned, since congenital malformations can occur even following secondary maternal infection.[4] However, reliable serological tests are available, especially CMV-G avidity assays. The data in Fig. 1 confirm other studies[29,30] showing that that the presence of CMV-M may not be indicative of recent primary infection, as most pregnant women with positive CMV-M had acquired CMV infection before pregnancy (128/141). Moreover, as it has been shown that behavioral counseling is more effective during pregnancy than in non-pregnant women,[19–21] we speculate that adherence to protective behavior may be more effective if women know they are seronegative for CMV. It remains to be determined if CMV testing should be proposed for all pregnant women, or restricted to high risk populations, and how it should be carried out. Overall, our results confirm that basic hygiene information given to seronegative pregnant women at the beginning of pregnancy has a positive impact.

The global burden of the disease in the USA and Europe is a reason for not only accelerating research on vaccines, but also on other ways of preventing congenital CMV disease.[26] Despite its large public health burden, current knowledge and awareness of congenital CMV infection among women of childbearing age seems very low.[11–13] Women deserve to be informed how they can reduce their risk of CMV infection during pregnancy, and our study demonstrates that hygiene counseling can be effective.

Conflict of interest

The authors declare no conflicts of interest.

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Ethical approval: The study was approved by the ethics committee (Comité de Protection des Personnes, Ile de France; International Review Board Approval CEROG-2008-011).

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