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A 2-year study on cytomegalovirus infection during pregnancy in a French hospital

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Objectives To evaluate the proportion of pregnant women agreeing to cytomegalovirus (CMV) serologic screening. To collect data on CMV infection during pregnancy.

Design Prospective study.

Setting During two years, all pregnant women were informed on CMV infection. If the patient agreed, serological testing was performed around 12 weeks of gestation (WG) and, if negative, redone around 36 WG.

Population Four thousand two hundred and eighty-seven pregnant women followed from 12 weeks to delivery.

Methods If the first CMV serologic test was negative, detailed hygiene information was given to the parents. Diagnosis of primary infection was based on the detection of CMV-G, CMV-M and low CMV-G avidity index. When maternal infection was confirmed, diagnosis of CMV congenital infection was done in the newborns by urine culture within the three days following birth. Crude infection-rate data consisted of the number of CMV infection cases and person-time units for both exposed to hygiene CMV information (12 to 36 WG) and unexposed pregnant women (first 12 WG).

Main outcome measures Rate of CMV seropositive and seronegative women. Rate of women agreeing for screening. Rate of primary infection. Rate of seroconversion. Number of CMV-infected newborns.

Results Among the 4287 women followed, 3792 were either seronegative or with an unknown immune status. 96.7% out of them agreed for screening. 53.2% were initially CMV-specific IgG negative. Primary infection was detected in nine women between 0 and 12 WG (0.46%) and seroconversion was diagnosed in five women between 12 and 36 WG (0.26%) (mid $P = 0.02$, 95% CI [1.07–13.6]).

Conclusions If clear information on CMV infection during pregnancy is given, patients frequently agree to screening. The rate of seroconversion after information, observed in this study, is low after counselling.

Keywords Cytomegalovirus, epidemiology, management, prenatal diagnosis, prevention, screening.

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Introduction

Cytomegalovirus (CMV) is the most frequent cause of congenital viral infections,[1] with an incidence of 0.5 to 1.0% of all live births, and the leading infectious cause of sensorineural deafness and mental retardation.[2] CMV fetal infection can develop following both primary and recurrent maternal infections. Vertical transmission rate is around 30% following primary infection.[3] Five to 10% of infected newborns are symptomatic at birth and among asymptomatic newborns, 10 to 15% will eventually show some developmental disorders, mainly sensorineural-hearing loss.[4] Although CMV infection during pregnancy is quite frequent, epidemiological data of this infection, in France, is scarce. Screening of CMV infection during pregnancy is debated, but is not recommended in France. However, it is recommended to give information about CMV infection to pregnant women (French National Agency for Accreditation and Evaluation in Healthcare, *ANAES* 2004). The current knowledge and awareness of congenital CMV

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infection among women is low.[5] In the United States, on the basis of CMV seroprevalence infection, the high number of women at risk and the significance of congenital disease, development of programs for CMV infection prevention are considered of considerable public health importance by the Centers for Disease Control and Prevention.[6] To date, vaccines against CMV are not available and treatments of CMV infection during pregnancy need to be assessed in randomised trials.[7,8] Therefore, it is important to determine whether modifying potentially risky parental behaviour reduces the rate of CMV maternal infections. Prevention of maternal seroconversion by giving hygiene information on CMV infection has been described by Adler et al. and appears to be effective, but only small groups were involved in their prevention programme.[9,10] Up to now, no study has been carried out to evaluate the efficiency of hygiene information given to a large population of pregnant women followed in the same obstetric care unit. Furthermore, despite its large public health burden, few women seem to have heard of congenital CMV and even fewer are aware of prevention strategies.[5]

Considering these statements, we undertook a 2-year period study (2005 and 2006) that aimed: (i) to evaluate the frequency of women agreeing for screening after information on the consequences of CMV infection during pregnancy; (ii) to collect epidemiological data on CMV infection and its consequences during pregnancy. Analysing our data, we noticed that this study gave also interesting preliminary informations considering the influence of hygiene counselling on the rate of maternal CMV primary infection.

Methods

CMV screening has been performed in our hospital for years after informed consent have been signed. The medical staff is trained to inform the patients on CMV infection. The analysis of this epidemiological cohort was undertaken to audit our medical practices and was approved by the ethic committee (Comité de Protection des Personnes, Ile de France; International Review Board Approval CEROG-2008-011) . Medical data were stored anonymously and protected according the CNILs recommendations (Commission Nationale Informatique et Liberté, authorisation numbers 1181076 and 444971).

Data on all patients who had their first medical visit in our obstetric department between 1 January 2005 and 31 December 2006 and followed until the end of their pregnancy were analysed retrospectively.

The first medical visit in our institution is 12.6 (± 0.7) weeks of gestation (WG). At that time, each pregnant woman was informed on the possible consequences of CMV primary infection and on the lack of scientific data concerning the importance of screening. If patients agreed to CMV screening, serological testing was performed after written informed consent was obtained. If this first CMV serologic test was negative (absence of CMV-specific IgG [CMV-G] and CMV-specific IgM [CMV-M]), written (standard script) and oral detailed hygiene information was given to the mother and to the father and a second test was performed at 35.4 (±1.4) WG. Protective behaviour mainly included frequent hand washing (i.e. after exposure to children's bodily fluids and diaper changes, handling dirty laundry, touching the children's toys and other objects and bathing the child), and avoiding intimate contact with the child (i.e. such as kissing on the mouth, sleeping together, sharing towels and washcloths and sharing food or drink). Wearing protective gloves was not recommended in our institution. There was neither home visit nor video demonstration of these recommendations. Except for patients with primary infection or seroconversion diagnosed during pregnancy, all women had standard management of pregnancy, including three systematic ultrasound examinations at 12, 22 and 32 WG. If primary infection was detected or if seroconversion occurred, close fetal ultrasound examination was systematically performed monthly and amniocentesis was discussed. In the particular case of infections diagnosed at 36 weeks, only a close ultrasound was performed, including transvaginal evaluation of the fetal brain.

CMV-G, CMV-M and CMV-G avidity assays were performed with commercially available tests (Liaison, DiaSorin, Saluggia, Italy). When CMV-G avidity index was found low or moderate, it was controlled with an in-house test using 6 M urea as denaturing agent as previously described.[11] Diagnosis of primary infection was based on the detection of CMV-G, CMV-M and low CMV-G avidity index. Seroconversion was defined by the absence of both CMV-G and CMV-M around 12 WG, and the presence of CMV-G around 36 WG. When CMV seroconversion was observed at 36 WG, it was possible to date 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, diagnosis of CMV congenital infection was performed in the newborns by urine culture within the three days following birth.

In our obstetric department, systematic screening of hearing loss is performed on all newborns.

Statistical analysis was performed using STATA 8.2™ software (Stata Corporation, College Station, TX, USA). We used Pearson chi-square test to compare proportions, Student *t*-test to compare age means and Mann–Whitney test to compare gravidity and parity between CMV-G positive and negative women. We calculated Mantel–Haenszel odds ratios adjusted for age. Crude infection-rate data consisted of the number of CMV infection cases and

person-time units for both exposed to hygiene CMV information (12–36 WG) and unexposed pregnant women (first 12 WG). Statistical significance of the incidence risk ratio was evaluated by an exact test based on the Poisson distribution (EPITAB commands).

Results

Among the 4287 pregnant women followed in our institution, 495 were known as CMV seropositive before the first visit to our centre and 3792 had unknown immune status or were known to be seronegative. In total, 3665 out of 3792 agreed for screening (96.7%) (Figure 1). Out of the 3665 women tested, 1714 were CMV-G positive and 1951 CMV-G negative, giving a seroprevalence of 46.8% if only the women screened are taken into consideration or 53.1% (2209/4160), if the pregnant women who were seropositive before pregnancy are taken into account.

In France, it is not authorised to store ethnic data. This is why this information is not available.

Among the initially 1714 CMV-G positive patients, 98 were CMV-M positive (5.7%). Only nine out of the 98 CMV-M positive patients had a low CMV-G avidity index (9.2%) confirming primary infection within the first 12 WG, 76/98 had a high CMV-G avidity index (77.5%) excluding primary infection and 13/98 an intermediate CMV-G avidity index (13.3%). Concerning the 13 women who had intermediate CMV-G avidity index at their first visit, further investigations (analysis of stored serums, i.e. serums stored for HCG evaluation at the beginning of pregnancy) showed that 12 of them were in fact infected before pregnancy, and 1 was lost for follow up after 12 WG. If we consider that the nine patients with a primary infection had a negative serology at 0 WG, the number of women who had never encountered the CMV at the very beginning of pregnancy is the number of seronegative women at 12 WG (1951) plus nine, that is to say 1960. The rate of CMV infection during the 12 first WG is therefore 0.46% (9/1960). Only five, out of the 1951 patients who were CMV-G negative at around 12 WG, demonstrated seroconversion between 12 and 36 WG (Figure 1).

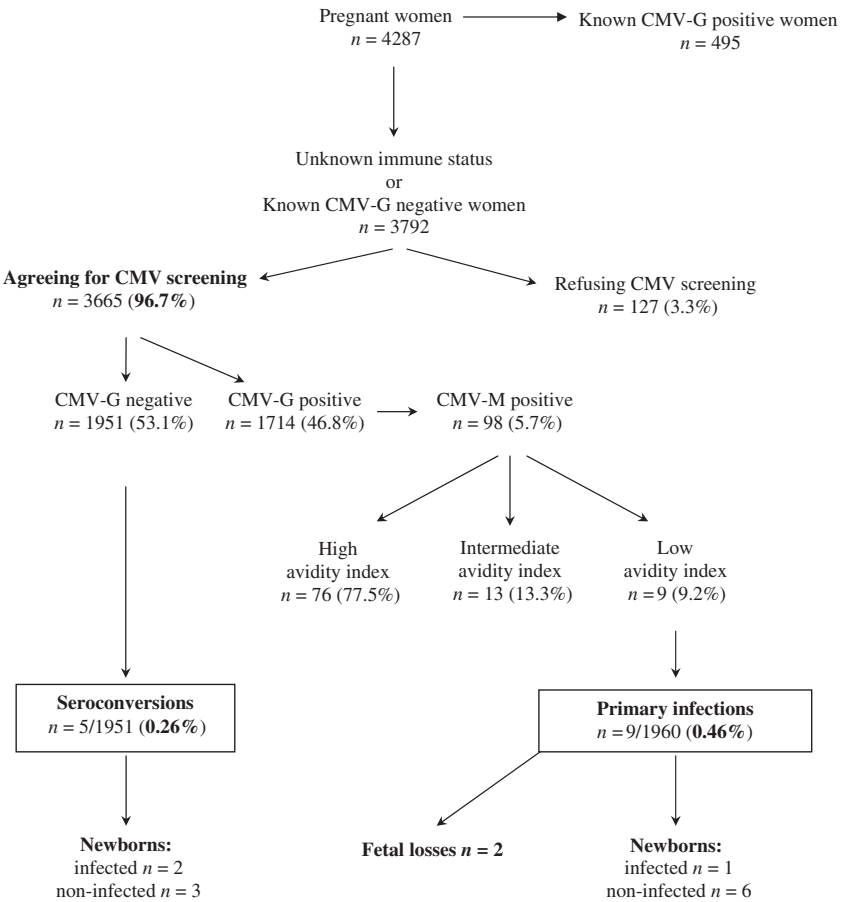

Figure 1. Overall CMV serological results of the 4287 pregnant women followed in our Obstetric department and outcome of pregnancy of those who demonstrated CMV primary infection or seroconversion.

The rate of CMV infection between 12 and 36 WG is therefore 0.26% (5/1951). Out of the 14 cases of maternal CMV infection, 13 occurred in high risk women: child nurses ($n = 5$), medical doctors ($n = 2$), women with a child <3 years of age at home ($n = 10$). Two nurses out of five and the two medical doctors had a child <3 years at home.

Among the nine women with primary infection, there were two spontaneous fetal losses: one at 12 WG and the other at 18 WG. In this latter case, twin fetal loss occurred following ultrasound guided reduction from three to two fetuses. There was no histological proof of CMV infection in any of the fetuses. For the 12 other women (seven primary infections before 12 WG with a viable fetus and five seroconversions between 12 and 36 WG), ultrasound examinations, systematically performed monthly after CMV primary infection or seroconversion, were normal until delivery. Amniocentesis was discussed in each case, but was only performed twice. From the 12 women who demonstrated CMV infection during pregnancy, nine babies were born noninfected and only three were born infected: two to women who seroconverted and one to a woman with primary infection before 12WG. The child born to the latter woman had petechias 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 (13, 14 and 23 months). Furthermore, no ultrasound abnormality related to fetal CMV infection was observed for any of the fetuses of the 4287 pregnant women included in this study.

In total, among the 3665 screened women over the 2-year period, nine confirmed primary infection, which occurred within the first 12.6 ± 0.6 WG. Among the 1951 seronegative women at 12 WG, five were detected seropositive at 35.4 ± 1.4 WG. Retrospective analysis of stored serum samples (collected for other analysis, i.e. toxoplasmosis serology according to the French legislation) showed that seroconversions occurred equally during the 2nd and the 3rd trimesters of pregnancy at, respectively, 18, 20, 24, 27 and 31 WG. According to these data, the infection rate between 12 and 36 WG is of 0.01 per 100 pregnant woman-week, and is significantly lower than the infection rate before 12 WG which is of 0.04 per 100 pregnant woman-week (mid $P = 0.02$, 95% CI [1.07–13.6]).

Discussion

We noticed that a great majority of pregnant women accept serologic testing (96.7%), Seroprevalence in our obstetric department (53.1%) was found similar to those reported by other studies in Europe[11–15]

Our study was not designed to study predictive factors for CMV seroprevalence; however, we found that the proportions of gravidity >2 and parity >1 were higher for CMV-G positive women, independently of age. These results are concordant with another French study[12]. Indeed, these findings certainly reflect increase exposure to CMV for women who took care of their own previous children.

Considering at-risk professional occupations, there were no differences between both CMV-G positive or CMV-G negative groups. Nevertheless, we noticed that among the 14 women who demonstrated CMV infection during pregnancy, 13 were at high risk of CMV infection (multipara, nurses, medical doctor) and nine were infected before hygiene counselling. Hygiene information are all related to handling young children, therefore counselling would be irrelevant to women with no young children at home or at work. However, these patients are at low risk for acquiring CMV during pregnancy.

As a randomised study would not have been ethically acceptable, all pregnant women of our cohort were informed of the possible consequences of acquiring CMV during pregnancy. During the 12 first WG, before the first visit in our obstetric department and before hygiene counselling, confirmed primary infection had occurred in nine women and during the following 24 WG, only five women demonstrated seroconversion. Without neither information on the consequences of CMV infection nor hygiene counselling, we suppose we would have expected the same quarterly incidence of seroconversion during these following 24 weeks, that is to say twice as many more seroconversions between 12 and 36 WG than in the first 12 WG. The lower incidence of CMV infection after 12 WG could be partly because of other factors leading to a lower exposition to the virus during the 2nd and 3rd trimesters of pregnancy (i.e. stopping professional activities). These potential confounding factors may not represent a bias in our analysis as the rate of seroconversion was identical during 2nd and 3rd trimester (Table 1). Moreover, the rate of seroconversion we observed is very low (0.26%) compared to the rate of previously published series (0.9 to 1.4%), in countries where CMV seroprevalence is similar to ours (51.5–53.9%) [11–15].

Overall, even if these preliminary results must be confirmed in further larger studies, it seems that hygiene information has a positive impact and could significantly reduce the incidence of CMV maternal infection during pregnancy. No cost-effectiveness analysis was performed and the psychological impact of information and anxiety generated by screening has not been evaluated. Furthermore, in our study two kinds of CMV infections may have been missed: those which occurred in previously CMV-G positive women (maternal reinfection/reactivation) and those who occurred after the last serologic analysis. However, the only way to diagnose these cases would have been to screen all newborns for CMV infection.

Table 1. Demographic datas on gravidity, parity, maternal age and at-risk professional occupation

	CMV-G positive (n = 1714)	CMV-G negative (n = 1951)	P
Gravidity	2.28 (0–14)	2.05 (1–11)	
Proportion of gravidity>2	34.4%	28.1%	3×10^{-5}*
Parity	0.7 (0–11)	0.6 (0–6)	
Proportion of parity>1	17.3%	13.2%	10^{-3}*
Mean maternal Age in years (standard deviation)	30.6 (5.7)	31.4 (4.7)	10^{-6}**
Professional at risk patients***	19.7%	19.0%	0.64

*Pearson chi-square test.
**Student's t test.
***Professional at-risk patients for acquiring CMV during pregnancy is defined as medical doctors, nurses, and women who work with young children.
$P < 0.05$ is considered as statistically significant.

As vaccines against CMV are not available and treatments of CMV infection during pregnancy are only under study[7,8], it is important to determine whether modifying potential risky parental behaviour, reduces the rate of maternal CMV primary infection. The first description of giving hygiene information to decrease the rate of maternal infection has been published by Adler *et al.* in a high risk population.[9,10] They concluded that intervention may be highly effective for preventing CMV infection for seronegative women who already know they are pregnant. However, these studies are different from ours (i) as there were carried out on small populations at high risk of contamination and (ii) as adherence to hygiene measures was controlled by home visits. Indeed, our results rely on a population-based study, and the protective behaviour recommended was lighter (protective gloves were not recommended and there was no control by home visits). No attempts were made to ascertain whether the counselling regarding hygiene practices was observed.

In the United States, it is estimated that 27 000 new CMV infections occur among seronegative pregnant women each year.[16] The global disease burden is reason for accelerating research on vaccines and other interventions for preventing congenital CMV disease. There is an urgent need for interventions that could reduce the substantial burden of this overlooked disease. Despite its large public health burden, few women seem to have heard of congenital CMV infection and even fewer are aware of prevention strategies[5] Given the present state of our knowledge, women deserve to be informed about how they can reduce their risk of CMV infection during pregnancy[17] and we do believe that changing behaviours may be effective in a general population.

Conclusion

Our results suggest that (i) if clear information on CMV infection during pregnancy is given, patients very frequently agree for screening; (ii) seroprevalence reported is similar to that reported in Northern Europe; (iii) counselling of pregnant women could be effective. This study, together with those analysing prenatal treatments, opens the door to larger studies on the management of CMV congenital infection. It remains to determine if CMV testing has to be proposed to all pregnant women or restricted to high risk populations and how. This question is still debated in the scientific community.

Disclosure of interest

We declare no conflict of interest.

Contribution to authorship

All authors fulfilled all conditions required for authorship and approved the submission. L. Grangeot-Keros designed the project, set up the study and her contribution was important in revising the manuscript. O. Picone and C. Vauloup-Fellous co-wrote the manuscript. O. Picone, C. Vauloup-Fellous, L. Grangeot-Keros and AG. Cordier actively participated to the conduct of the research. O. Picone and MV. Senat were in charge of the specific management of the CMV-infected patients. L. Grangeot-Keros and C. Vauloup-Fellous were in charge of the serologic analysis. AG. Cordier collected the data concerning all pregnant women enrolled in the study. I. Parent du Châtelet performed the statistical analysis and participated to the critical analysis of the manuscript. R. Frydman is the head of the obstetric department and approved the final submitted version of the manuscript.

Details of ethics approval

Medical data were anonymously stored and protected according to CNILs recommendations (Commission Nationale Informatique et Liberté, authorisation numbers 1181076 and 444971). The analysis of this epidemiological cohort was undertaken to evaluate our medical practices and was approved by the ethic committee (Comité de Protection des Personnes, Ile de France and International Review Board Approval CEROG-2008-011).

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