CORRESPONDENCE

Primary Human Cytomegalovirus (HCMV) Infection in Pregnancy

by Dr. med. Horst Buxmann, Prof. Dr. med. Dr. rer. nat. Klaus Hamprecht, Prof. Dr. med. Matthias Meyer-Wittkopf, and em. Prof. Dr. med. Klaus Friese in issue 4/2017

Protecting the Health of Pregnant Women

As an occupational physician, I thank Buxmann et al. for their review article, which excellently summarized what is currently known about cytomegalovirus infection (1). When pregnant women are counselled in the workplace, they receive far too little information about infection pathways of cytomegalovirus (CMV) and opportunities for preventing infection.

For CMV infections in the workplace setting, however, meaningful studies for the German speaking region are lacking. Because of this lack of data, the recommendations of the statutory maternity protection authorities with regard to employment restrictions for expectant mothers are heterogeneous. Some federal states have banned all pregnant women who are CMV seronegative from contact with children younger than 3 years, which means one in two pregnant women in this setting.

Solid supporting data are lacking not only at the health political level but also at the corporate level. In order to gain initial insights into the risk of CMV for daycare workers, CMV sero-status and risk factors of pregnant nursery workers from children's day care centers in Hamburg (n = 509), collected between 2010 and 2013, were compared with data from women donating blood for the first time (n = 14 358). The entire group of daycare workers had a higher seroprevalence (SP) depending on age than the blood donors, but there was no difference between the teachers and the subgroup of blood donors with a history of pregnancy and living in urban areas (SP 54.6 versus 53.9 %; odds ratio 0.9; 95% confidence interval [0.8; 1.2] (2, 3).

The results confirm those from studies from other European countries, which found a CMV infection risk that was comparable to infection risks in the private sphere—except for the first two years in work (4). CMV seropositive pregnant women working in exposed areas such as neonatology, obstetrics, children's day cares, oncology, and intensive care will have to be made aware of targeted hygiene measures on a continuing basis. Current longitudinal studies of the CMV infection risk in the workplace and of occupational prevention strategies are needed to provide competent advice.

DOI: 10.3238/arztebl.2017.0504a

REFERENCES

1. Buxmann H, Hamprecht K, Meyer-Wittkopf M, Friese K: Primary human cytomegalovirus (HCMV) infection in pregnancy. *Dtsch Arztebl Int* 2017; 114: 45–52.
2. Stranzinger J, Kindel J, Henning M, Wendeler D, Nienhaus A: Prevalence of CMV infection among staff in a metropolitan children's hospital—occupational health screening findings. *GMS Hyg Infect Control* 2016; 11: Doc20.
3. Stranzinger J, Kozak A, Schilgen B, et al.: Are female daycare workers at greater risk of cytomegalovirus infection? A secondary data analysis of CMV seroprevalence between 2010 and 2013 in Hamburg, Germany, *GMS Hyg Infect Control* 2016; 11: Doc09

4. Stelma FF, Smismans A, Goossens VJ, Bruggeman CA, Hoebe CJ: Occupational risk of human cytomegalovirus and parvovirus B19 infection in female day care personal in the Netherlands, a study based on seroprevalence. *Eur J Clin Microbiol Infect Dis* 2009; 28: 393–7.

Dr. med. univ. Johanna Stranzinger

Berufsgenossenschaft für Gesundheitsdienst und Wohlfahrtspflege
Grundlagen der Prävention und Rehabilitation
Fachbereich Arbeitsmedizin
Hamburg
johanna.stranzinger@bgw-online.de

Conflict of interest statement

The author declares that no conflict of interest exists.

Primary Prevention Ahead of Pregnancy

In their important article (1), the authors present a concept for prevention in pregnancy and simultaneously highlight the concept's limitations, which arise from the particularities of infection with cytomegalovirus.

- The timing of the expectant mother's primary infection before or during pregnancy is crucial for assessing any teratogenic risks.
- Determining the exact time at which the infection was acquired uses laboratory diagnostics in pregnancy; the authors also recommend determining the anti-CMV-IgM titer (*Figure 2* in the article) as an obligatory component. This parameter may become non-specifically positive in the setting of upper respiratory tract infections (common cold).
- Whether the fetus is infected can only be determined from the second trimester onward by using invasive prenatal diagnostic evaluation.
- Treatment has not been shown to be unequivocally effective.
- The most common complication (progressive hearing loss in infancy) is not captured.

A screening program with seasonal fluctuations would put at least 0.5–4% of pregnant women (the estimated rate of maternal primary infection in pregnancy) under psychological pressure because of findings that will require further investigation. Some parents decide on a termination of pregnancy in the first trimester without waiting for the diagnostic evaluation of the fetus (8%, according to Daiminger [2]).

Pre-pregnancy prevention should be discussed as an additional option, in my opinion (3). This could be combined with family planning advice or checking for whether the rubella vaccine has been received by a woman of childbearing age, and it could—in addition to education about infection pathways and hygiene rules—be restricted to determining CMV-IgG.

A seropositive partner can be infectious if he is going through a primary infection (handling infants, promiscuity) or is taking immunosuppressants. The risk for CMV infection is rather small in stable relationships (4). It could be reduced further by advising and informing a couple before a pregnancy.

DOI: 10.3238/arztebl.2017.0504b

REFERENCES

1. Buxmann H, Hamprecht K, Meyer-Wittkopf M, Friese K: Primary human cytomegalovirus (HCMV) infection in pregnancy. *Dtsch Arztebl Int* 2017; 114: 45–52.
2. Daiminger A, Bäder U, Enders G: Pre- and periconceptional primary cytomegalovirus infection: risk of vertical transmission and congenital disease. *BJOG* 2005; 112: 166–72.
3. Reichman O, Miskin I, Sharoni L, et al.: Preconception screening for cytomegalovirus: an effective preventive approach. *BioMed Research Int* 2014; article ID 135416: 1–4.
4. Kling C, Kabelitz D: Congenital HCMV and assisted reproduction: why not use the chance for primary screening? *Arch Gynecol Obstet* 2015; 291: 1205–11.

Dr. med. Christiane Kling

Ärztin für Allgemeinmedizin, Zusatz Medizinische Genetik
Hamburg/Kiel
ckling@fennerlabor.de

Conflict of interest statement

The author declares that no conflict of interest exists.

In Reply:

We thank Stranzinger and Kling for their positive comments, the valuable additional points, and the critical remarks in response to our article (1).

Stranzinger quite rightly points out the fact that in the German-speaking region, insufficient data exist on congenital infections with human cytomegalovirus (HCMV) in the context of occupational legal aspects. The subsequent problem of primary infection with HCMV in pregnancy is—in addition to important medical aspects—of economic relevance for those affected because of restrictions on employment in parts. Unfortunately, recommendations for maternity protection and employment protection vis-à-vis potential viral exposure at work have not yet been harmonized across Germany's federal states.

The review article in *Deutsches Ärzteblatt* was subject to restrictions on space and scope. For this reason, the risks of HCMV transmission in the workplace was not included in our article (1).

We share Stranzinger's assessment, that pregnant women who work in areas with exposure to HCMV should be comprehensively informed about hygiene measures to prevent HCMV transmission; we also support her call for longitudinal studies to determine the risk of HCMV infection in workplaces. Extensive studies have been reported that investigated horizontal HCMV transmission from infants to pregnant women in the USA, but such data exist only marginally for Germany (2).

Kling is right in saying that the relative reported timing of the acquisition of the infection (before or around the time of conception, or in the 1–3 trimesters) can help to roughly categorize the potential risk for the manifestation of symptomatic congenital HCMV infection of the neonate. To this end, the primary infection of the mother is diagnosed by using a low concentration of HCMV-IgG and low HCMV-IgG avidity in mostly low HCMV-IgM indices. As explained in the 2014 S2k guideline for the diagnosis of viral infections in pregnancy by the Association of Scientific Medical Societies in Germany (*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften*, AWMF), any HCMV-IgM reactivity should be confirmed by using an immunoblot test. It is well known that HCMV-IgM reactivity is often non-specifically

persistent and can be detected co-reactively with other viral infections.

On the basis of a recent international consensus recommendation, universal HCMV antibody screening in pregnancy is not recommended (3). The authors advise conducting selective HCMV-IgG screening at the start of the pregnancy—as is customary in Israel, the US (Hawaii, Utah, Texas), Australia, and Belgium, as well as in population-based studies (Italy, France). The objective is to identify HCMV seronegative pregnant women at risk and to provide hygiene information/education to prevent viral transmission (and potential additional tests for HCMV-IgG).

Especially this population is at the greatest risk for symptomatic congenital HCMV infection of the neonate (4, 5), particularly in a country with a low prevalence of HCMV, such as Germany. The data do not allow a reliable estimate of the incidence of congenital HCMV infections as a result of recurring HCMV infection in pregnant women. Preconceptual HCMV antibody screening makes sense from the perspective of preimplantation diagnostic evaluation and is included in the AWMF guideline—in contrast to the international consensus recommendation. The 2014 AWMF guideline strongly recommends selective HCMV-IgG screening of women with occupational or private exposure owing to contact with infants, whereas it gives merely a low-level recommendation for universal HCMV-IgG screening.

DOI: 10.3238/arztebl.2017.0505

REFERENCES

1. Buxmann H, Hamprecht K, Meyer-Wittkopf M, Friese K: Primary human cytomegalovirus (HCMV) infection in pregnancy. *Dtsch Arztebl Int* 2017; 114: 45–52.
2. Hamprecht K, Bissinger AL, Arellano-Galindo J, et al.: Intrafamilial transmission of human cytomegalovirus (HCMV): long-term dynamics of epitope-specific antibody response in context of avidity maturation. *J Clin Virol* 2014; 60: 119–26.
3. Rawlinson WD, Boppana SB, Fowler KB, et al.: Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. *Lancet Infect Dis* 2017. Doi: 10.1016/S1473-3099(17)30143-3. (Epub ahead of print).
4. Picone O, Vauloup-Fellous C, Cordier AG, et al.: A series of 238 cytomegalovirus primary infections during pregnancy: description and outcome. *Perinatal Diagnosis* 2013; 33: 751–8.
5. Bilavsky E, Pardo J, Attias J, et al.: Clinical implications for children born with congenital cytomegalovirus infection following a negative amniocentesis. *Clin Infect Dis* 2016; 63: 33–8.

On behalf of the authors

Dr. med. H. Buxmann

Universitätsklinikum Frankfurt
Klinik für Kinder- und Jugendmedizin, Schwerpunkt Neonatologie
H.Buxmann.MD@web.de

Prof. Dr. med. Dr. rer. nat. K. Hamprecht

Universitätsklinikum Tübingen
Institut für Medizinische Virologie und Epidemiologie der Viruskrankheiten

Conflict of interest statement

Dr. Buxmann, Prof. Meyer-Wittkopf and Prof. Hamprecht are members of the Scientific Advisory Board of the online platform ICON (Initiative for the Prevention of Congenital HCMV Infections) and have received reimbursements of travel costs, congress and lecture fees related to their work in this role from Biotest AG, Dreieich, Germany.

In addition, Dr. Buxmann and Prof. Hamprecht have received research funding (third-party funding) from Biotest AG, Dreieich, Germany.

Prof. Hamprecht has also received reimbursement of continuing education and travel costs as well as lecture fees from Abbott, Roche and Siemens. He has made all lecture fees available to the Tübinger HCMV Congenital Study via a third-party funding account of the University Hospital Tübingen (UKT).