Clinical Microbiology and Infection 22 (2016) 818–820

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Letter to the Editor

Pregnancy outcomes and cytomegalovirus DNAaemia in HIV-infected pregnant women with CMV

Sir,

It is well known that cytomegalovirus (CMV) coinfection affects a large proportion of people with HIV, with a significant impact on disease progression and survival [1]. In HIV-CMV coinfected pregnant women, however, few studies have been conducted: maternal immunosuppression has been linked to a higher risk of CMV infant infection, and CMV DNAaemia to higher maternal and infant mortality [2,3]. Overall, little is known about pregnancy outcomes and CMV viraemia in CMV-coinfected pregnant women with HIV. To further explore this issue, the impact of CMV coinfection was evaluated on pregnancy outcomes in a national cohort of pregnant women with HIV, assessing in a study subsample the prevalence and correlates of CMV DNAaemia in HIV-CMV coinfected pregnant women.

Data from the Italian National Program on Surveillance on Antiretroviral Treatment in Pregnancy were used [4], considering all HIV-infected women with known CMV serostatus. The main pregnancy outcomes were compared between women with and without positive serology for CMV, and plasma CMV-DNA levels were evaluated in a subset of CMV-positive women who had given specific consent to virological evaluations and had evaluable plasma samples. The cases were analysed retrospectively, and no systematic screening for CMV infection was conducted in infants. Ethics approval was obtained from the ethics committee of the I.N.M.I. Lazzaro Spallanzani in Rome; ref. deliberations: 578/2001 (28 September 2001) and 7/2003 (26 February 2003). Plasma CMV-DNA was quantified with the kPCR PLX Cytomegalovirus DNA assay (Siemens Healthcare) using the VERSANT kPCR Molecular System (Siemens), with a detection limit of 214.6 (2.33 log) IU/mL. Quantitative data were compared by the Mann-Whitney *U* test and proportions by the chi-square test, with OR and 95% CI calculated. A *p*-value below 0.05 was considered to be significant, using for all analyses the SPSS software, version 22.0 (IBM Corp, Released 2013, Armonk, NY, USA).

As of 21 March 2016, among 2250 pregnancies with available information on CMV serostatus (62% of all cases in the database, including ongoing pregnancies and cases lost to follow-up), 1490 were CMV antibody-positive (66.2%). Women with and without positive serology for CMV were similar for age, CD4 counts, CDC-HIV disease stage, parity, antiretroviral treatment experience, and treatment status at conception. No differences between the two groups were found for the main pregnancy outcomes, represented by miscarriage or fetal demise, preterm delivery, low (<2500g) or very low (<1500g) birthweight, intrauterine growth restriction (gender- and gestational age-adjusted Z-score for birthweight <10° percentile), major birth defects, delivery complications, and HIV transmission (Table 1). Among 1126 infants from CMV-positive mothers with available information on clinical status, three neonatal cases of CMV infection were reported.

Among the 1490 women positive for CMV antibodies, 123 (8.3%) had available plasma samples collected during pregnancy, usually (90.2%) after the first trimester, which were evaluated for CMV-DNA quantitation. None of these women had clinical signs of new viral infection or viral reactivation during pregnancy. Only four of them (3.3%) had positive CMV DNAaemia in plasma, all at very low levels (range 2.35–2.61 log IU/mL). None of these four women had low (<200/mm^3) CD4 counts (range 270–852), and all had normal pregnancy outcomes, with no preterm delivery, low birthweight, birth defects, CMV or HIV transmission reported. Interestingly, all the four mothers had detectable HIV in plasma at third trimester (range 99–20 004 copies/mL).

This study showed that in a large cohort of pregnant women with HIV, roughly two-thirds had positive serology for CMV, with no adverse consequences of coinfection on the main pregnancy outcomes. This rate is almost identical to that observed in two different studies conducted among a general population of pregnant women in Northern and Southern Italy, who showed prevalences of positive CMV serology of 68.3% (1925/2817) and 65.9% (595/797), respectively [5,6], suggesting similar CMV prevalence for HIV-negative and HIV-positive pregnant women. It was also shown in a nested evaluation that among pregnant women with HIV with positive serology for CMV and no signs of primary infection, a small proportion (4/123, 3.3%) have detectable CMV DNAaemia, usually at low levels. This figure is consistent with published data in an HIV-CMV coinfected African population, in whom rate of detectable CMV in plasma was 4.8% (7/146) [7], suggesting slightly higher rate of CMV DNAaemia among pregnant women with HIV compared with the general population. In a previous Italian study on a general population of CMV IgG-positive pregnant women with no evidence of primary infection, 0.5% (4/774) had positive, low-level CMV DNAaemia [8]. A similar rate (2/134, 1.4%) was found in an unselected population of Turkish pregnant women [9]. Detectable low-level CMV DNAaemia could represent either subclinical viral reactivation or the terminal phase of blood viral clearance after a recent primary infection. It is unknown whether partial immunosuppression in pregnant women with HIV may be responsible for low-level CMV replication and detectable DNAaemia, and it was not possible to define timing of CMV infection by antibody avidity testing or evaluation of CMV-specific IgM. In any case, asymptomatic maternal CMV DNAaemia in a context of relatively preserved CD4 counts seems to represent for pregnant women

http://dx.doi.org/10.1016/j.cmi.2016.06.017

Table 1
Characteristics and pregnancy outcomes according to CMV serostatus

Women's characteristics	CMV-positive		CMV-negative		CMV-positive	CMV-negative	*p*-value[a]
	N				Median values (IQR)		
Age, years (*n*: 2245)	1486		759		33 (29–36)	33 (28–37)	0.924
CD4 cell count, cells/mm^3 (n: 1453)[b]	998		455		437 (297–591)	425 (289–612)	0.978
	n/N	%	*n/N*	%			
At least one previous pregnancy (*n*: 2218)	1090/1467	74.3	551/751	73.4			0.636
History of AIDS-defining events (*n*: 2220)	84/1470	5.7	45/750	6.0			0.785
Antiretroviral-treatment experienced (*n*: 2185)	929/1447	64.2	504/738	68.3			0.057
On treatment at conception (*n*: 2225)	777/1475	52.7	390/750	52.0			0.762
Pregnancy outcomes					OR[c]	OR 95% CI	
Miscarriage or fetal demise (*n*: 1941)	95/1313	7.2	56/628	8.9	0.797	0.564–1.125	0.196
Preterm delivery (*n*: 1672)	234/1152	20.3	108/520	20.8	0.972	0.753–1.256	0.830
Low birthweight (<2500 g) (*n*: 1576, twins included)	250/1082	23.1	101/494	20.4	1.169	0.901–1.517	0.239
Very low birthweight (<1500 g) (*n*: 1576, twins included)	37/1082	3.4	11/494	2.2	1.555	0.786–3.074	0.205
Small by gestational age (<10th percentile) (*n*: 1516, singletons only)	130/1034	12.6	53/482	11.0	1.164	0.829–1.634	0.381
Complications of delivery[d] (*n*: 1606)	85/1100	7.7	37/506	7.3	1.062	0.711–1.586	0.771
Major birth defects (*n*: 1616)	39/1108	3.5	17/508	3.3	1.054	0.590–1.881	0.860
HIV transmission (*n*: 1235)	14/857	1.6	8/370	2.1	0.768	0.319–1.847	0.556

IQR, interquartile range; ARV, antiretroviral therapy.
[a] Mann-Whitney *U* test for quantitative variables and chi-square test for categorical variables.
[b] Second trimester.
[c] Reference category: CMV-positive.
[d] Usually represented by surgical wound infections and fever.

with HIV an infrequent condition not associated with major clinical consequences.

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Transparency declaration

None to declare. This work was supported in the past by public research grants (ref.: H85E08000200005) from the Italian Medicines Agency (AIFA). No funding was received from any of the following organizations: National Institutes of Health (NIH); Wellcome Trust; and the Howard Hughes Medical Institute (HHMI).

Acknowledgements

We thank Cosimo Polizzi and Alessandra Mattei of the Istituto Superiore di Sanità in Rome, Italy, for providing technical secretarial for this study. No compensation was received for this contribution.

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18 April 2016
Available online 9 July 2016

Editor: L. Kaiser