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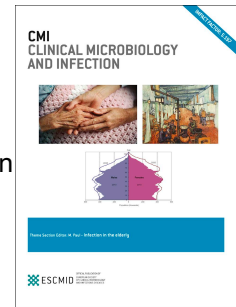
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Pregnancy outcomes and cytomegalovirus DNAemia in HIV-infected pregnant women with CMV.

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Running title: **Correlates of CMV coinfection in pregnant women with HIV**

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30 **Sir**, it is well known that cytomegalovirus (CMV) coinfection affects a large proportion of people
31 with HIV, with a significant impact on disease progression and survival [1]. In HIV-CMV coinfecting pregnant
32 women, however, few studies have been conducted: maternal immunosuppression has been linked to a
33 higher risk of CMV infant infection, and CMV DNAemia to higher maternal and infant mortality [2-3].
34 Overall, little is known about pregnancy outcomes and CMV viremia in CMV-coinfecting pregnant women
35 with HIV. In order to further explore this issue, we evaluated the impact of CMV coinfection on pregnancy
36 outcomes in a national cohort of pregnant women with HIV, assessing in a study subsample the prevalence
37 and correlates of CMV DNAemia in HIV-CMV coinfecting pregnant women.

38 Data from the Italian National Program on Surveillance on Antiretroviral Treatment in Pregnancy were
39 used [4], considering all HIV-infected women with known CMV serostatus. We compared the main
40 pregnancy outcomes between women with and without positive serology for CMV, and evaluated
41 plasma CMV-DNA levels in a subset of CMV-positive women who had given specific consent to
42 virologic evaluations and had evaluable plasma samples. The cases were analyzed retrospectively, and
43 no systematic screening for CMV infection was conducted in infants. Ethics approval was obtained
44 from the Ethics Committee of the I.N.M.I. Lazzaro Spallanzani in Rome; ref. deliberations: 578/2001
45 (September 28, 2001) and 7/2003 (February 26, 2003). Plasma CMV-DNA was quantified with the kPCR
46 PLX[®] Cytomegalovirus DNA assay (Siemens Healthcare) using the VERSANT[™] kPCR Molecular System
47 (Siemens), with a detection limit of 214.6 (2.33 log) IU/ml. Quantitative data were compared by the
48 Mann-Whitney U test and proportions by the chi-square test, with odds ratios (OR) and 95%
49 confidence intervals (CI) calculated. P values below 0.05 were considered significant, using for all
50 analyses the SPSS software, version 22.0 (IBM Corp, Released 2013, Armonk, NY, USA).

51 As of March 21, 2016, among 2250 pregnancies with available information on CMV serostatus (62% of all
52 cases in the database, including ongoing pregnancies and cases lost to follow up), 1490 were CMV
53 antibody-positive (66.2%). Women with and without positive serology for CMV were similar for age, CD4
54 counts, CDC-HIV disease stage, parity, antiretroviral treatment experience and treatment status at
55 conception. No differences between the two groups were also found for the main pregnancy outcomes,
56 represented by miscarriage or fetal demise, preterm delivery, low (<2500g) or very low (<1500g)
57 birthweight, intrauterine growth restriction (gender- and gestational age-adjusted Z-score for birthweight
58 <10[°] percentile), major birth defects, delivery complications, and HIV transmission (Table 1). Among 1126
59 infants from CMV-positive mothers with available information on clinical status, three neonatal cases of
60 CMV infection were reported.

61 Among the 1490 women positive for CMV antibodies, 123 (8.3%) had available plasma samples collected
62 during pregnancy, usually (90.2%) after the first trimester, that were evaluated for CMV-DNA quantitation.

63 None of these women had clinical signs of new viral infection or viral reactivation during pregnancy. Only
64 four of them (3.3%) had positive CMV DNAemia in plasma, all at very low levels (range: 2.35-2.61 log
65 IU/ml). None of these four women had low (<200/mm³) CD4 counts (range: 270-852), and all had normal
66 pregnancy outcomes, with no preterm delivery, low birthweight, birth defects, CMV or HIV transmission
67 reported. Interestingly, all the four mothers had detectable HIV in plasma at third trimester (range: 99-
68 20004 copies/ml).

69 This study showed that in a large cohort of pregnant women with HIV, roughly two thirds had positive
70 serology for CMV, with no adverse consequences of coinfection on the main pregnancy outcomes. This rate
71 is almost identical to that observed in two different studies conducted among a general population of
72 pregnant women in Northern and Southern Italy, that showed prevalences of positive CMV serology of
73 68.3% (1925/2817) and 65.9% (595/797), respectively [5,6], suggesting similar CMV prevalence for HIV-
74 negative and HIV-positive pregnant women. We also showed in a nested evaluation that among pregnant
75 women with HIV with positive serology for CMV and no signs of primary infection, a small proportion
76 (4/123, 3.3%) have detectable CMV DNAemia, usually at low levels. This figure is consistent with published
77 data in an HIV-CMV coinfecting African population, where rate of detectable CMV in plasma was 4.8%
78 (7/146) [7], suggesting slightly higher rate of CMV DNAemia among pregnant women with HIV compared to
79 the general population. In a previous Italian study on a general population of CMV IgG-positive pregnant
80 women with no evidence of primary infection, 0.5% (4/774) had positive, low-level CMV DNAemia [8]. A
81 similar rate (2/134, 1.4%) was found in an unselected population of Turkish pregnant women [9].
82 Detectable low-level CMV DNAemia could represent either subclinical viral reactivation or the terminal
83 phase of blood viral clearance after a recent primary infection. It is unknown whether partial
84 immunosuppression in pregnant women with HIV may be responsible for low-level CMV replication and
85 detectable DNAemia, and we were unable to define timing of CMV infection by antibody avidity testing or
86 evaluation of CMV-specific IgM. In any case, asymptomatic maternal CMV DNAemia in a context of
87 relatively preserved CD4 counts seems to represent for pregnant women with HIV an infrequent condition
88 not associated with major clinical consequences.

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116 **Conflicts of interest:**

117 None to declare. None of the authors has a commercial or other association, financial interest, activity,
118 relationship or association that might pose a conflict of interest. The corresponding author had full access to all
119 the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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125 **Contribution to authorship**

126 MF designed the study, drafted and finalised the manuscript and was responsible for statistical analysis;
127 MFP and RA performed virological analyses on plasma samples and contributed to manuscript finalisation;
128 AdA, AM, ET, CP, GG, GN, GM, SD, IC, MS and MR substantially contributed to clinical activities, acquisition
129 of data and to critical revision of the manuscript. All the authors gave approval to the final version to be
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137 **References**

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162 herpes simplex virus 2, human papillomavirus 16-18 in Turkish pregnant. *Braz J Infect Dis*. 2010;14: 569-74.

Table 1. Characteristics and pregnancy outcomes according to CMV serostatus.

<i>Women's characteristics</i>	CMV-positive		CMV-negative		CMV-positive	CMV-negative	<i>P</i> 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
<i>Pregnancy outcomes</i>					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 (<10 th 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

OR = odds ratio; CI = Confidence interval; IQR = interquartile range; ARV = antiretroviral therapy.

^a Mann-Whitney *U* test for quantitative variables and Chi-square test for categorical variables. ^b 2nd trimester. ^c Reference category: CMV-positive. ^d Usually represented by surgical wound infections and fever.