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Influence of Parity and Sexual History on Cytomegalovirus Seroprevalence among Women 20-49 Years-old in the United States, 1999-2004

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Abstract

Objectives—To assess the influence of parity, as a proxy for exposure to children, and sexual history on cytomegalovirus (CMV) seroprevalence among women in the United States.

Methods—We analyzed data of 3710 women 20-49 years-old who were tested for CMV IgG antibodies in the 1999-2004 National Health and Nutrition Examination Survey, a nationally representative, cross-sectional survey of the non-institutionalized U.S. population. We performed logistic regression to determine independent variables associated with CMV seroprevalence.

Results—In age-adjusted univariate analysis, women who had given birth to ≥1 child had a higher overall CMV seroprevalence (66.0%; 95% confidence interval [CI]: 63.1-68.9%) compared to those who had not (49.0%; 95% CI: 44.4-53.7%) ($p<0.001$). Higher CMV seroprevalence was independently associated with increasing number of live births (adjusted Odds Ratio [aOR]=1.2, 95%CI=1.1-1.3, for each additional live birth), age at first sexual intercourse <18 vs. ≥18 years (aOR=1.3, 95%CI=1.1-1.6), number of life time sexual partners ≥10 vs. <10 (aOR=1.4, 95%CI=1.1-1.9), and herpes type II positivity (aOR=1.9, 95%CI=1.5-2.6) after controlling for age group, race/Hispanic origin, place of birth, poverty index ratio, and education level ($p<0.05$).

Conclusions—In this population-based sample of U.S. women of reproductive age, parity and sexual exposures were independently associated with higher CMV seroprevalence.

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CONFLICT OF INTEREST

The authors have no conflict of interest relevant to this article to disclose.

DISCLAIMER The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Keywords

cytomegalovirus; women of reproductive age; seroprevalence

INTRODUCTION

An estimated 0.7% or 28,000 children are born with congenital cytomegalovirus (CMV) infection annually in the United States [1]. Mother-to-fetus transmission, congenital CMV disease at birth and permanent disabilities due to congenital CMV infection are more likely when CMV infection during pregnancy occurs in CMV seronegative women, but can result from non-primary infections (reinfection or reactivation) in CMV seropositive women [2]. In the United States, the overall CMV IgG seroprevalence among women 12-49 years-old is 57.9% [3]. The estimated annual seroconversion rate among the general population of pregnant women is 2.3%, but is approximately 10 times higher among parents with a child shedding CMV [4].

Previous studies have shown that women caring for young children and with recent onset of sexual activity are at greatest risk of having an infant with congenital CMV infection, with adolescent mothers likely disproportionally affected by the disease burden caused by congenital CMV infection [5, 6]. However, the highest birth rates among U.S. women are observed in their 20s and early 30s. The extent to which these women remain susceptible to primary CMV infections throughout successive pregnancies is not well understood. We assessed the influence of parity, as a proxy for exposure to children, and sexual history on CMV seroprevalence among women 20-49 years-old in the United States.

METHODS

The National Health and Nutrition Examination Survey (NHANES) is a nationally representative, cross-sectional survey of the non-institutionalized U.S. population conducted by the Centers for Disease Control and Prevention since the 1970s. Data collection consists of: 1) a household screener to determine eligibility of any household members for the interview or examination; 2) an interview of eligible sample person to collect person-level data on demographics, health, and nutrition, and household information; and 3) a physical examination which includes collection of specimens for laboratory testing. Detailed methods of the NHANES have been published elsewhere [7]. The National Center for Health Statistics Research Ethics Review Board, Centers for Disease Control and Prevention, reviewed and approved all protocols for the conduct of NHANES 1999-2004. All participants provided written informed consent, including consent to have their blood, urine, and saliva specimens stored for future studies [7]. CMV-specific IgG antibody testing was performed in stored sera from NHANES 1999-2004, using ELISA (Quest International, Inc., Miami FL) [8], and results were added to the NHANES database which is publicly available.

A previous analysis of the 1999-2004 NHANES has shown that CMV seroprevalence was independently associated with older age, female sex, low household income, high household crowding, low education, and foreign country of birth [9]. We focused our analysis on women age 20-49 years because complete risk factor data were not available for women age

<20 years. We calculated seroprevalence for CMV IgG among women, overall and by age group (20-29, 30-39, 40-49 years), race/Hispanic origin, country of birth, household income and index ratio of family income to poverty, insurance status, education level, household crowding, age when had first live birth, parity (number of live births), and sexual history variables. Race/Hispanic origin was based on the respondents' self-assessment and categorized as non-Hispanic White, non-Hispanic Black, Mexican American, or other, which included non-Hispanic Asians, other Hispanics, and multi-racial. Country of birth was categorized as U.S. or non-U.S. The family income to poverty ratio, calculated by dividing family income by a poverty threshold specific for family size using the U.S. Department of Health and Human Services' 2012 poverty guidelines, was categorized as below (<1.0) or at or above the poverty threshold (≥1.0) [10]. Household crowding index was calculated dividing the household size by the number of rooms in the household, excluding bathrooms, and categorized as low (<0.5 persons per room), average (0.5-0.99 persons per room), or high (≥1 persons per room). Sexual history variables included age at first intercourse, number of lifetime sexual partners, herpes type II seropositivity, self-report of ever being diagnosed with any of four sexually transmitted diseases (chlamydia, gonorrhea, genital herpes, or genital warts), and any oral contraceptive use.

We calculated national estimates of CMV seroprevalence using the weights developed for the NHANES to represent the total civilian non-institutionalized U.S. household population and to account for oversampling and nonresponse to the household interview and physical examination [11]. There were 5291 women age 20-49 sampled in NHANES 1999-2004, of whom 4264 (80.6% of those sampled) were interviewed and 4042 (94.8% of those interviewed) were examined. Among those examined 3710 (91.8%) were tested for CMV IgG. Because the percent of those tested among those examined varied by <5% across levels of each variable analyzed we used the original NHANES exam weights without adjustment for non-response.

We estimated standard errors using Taylor Series Linearization, a design-based method which incorporates sample weights and accounts for stratification and clustering of the NHANES sample design [11]. We considered estimates unstable if: 1) the relative standard error (defined as the estimate divided by its standard error expressed as a percent) around the proportion of participants who were seropositive or seronegative was >30%; or 2) the estimate was based on <10 seropositive or seronegative persons. We used the exact binomial method to calculate 95% CIs. We evaluated pairwise differences between seroprevalence estimates and trends using a t-statistic from an orthogonal linear contrast procedure. We considered p-values <0.05 significant, with no adjustments for multiple comparisons.

We performed univariate analysis of CMV seroprevalence by sociodemographic variables, parity and sexual history variables. Because the age distribution varied by many of these variables and age was strongly associated with CMV seroprevalence, we standardized the estimates to the 2000 U.S. population age structure using the direct method to remove the confounding effect of age. We performed logistic regression to calculate adjusted odds ratios and 95% CI and determine independent variables associated with CMV seroprevalence. We included in the initial model all variables that were significant in the univariate analysis. Using backward stepwise elimination, we subsequently excluded variables no longer

significantly associated with CMV seroprevalence. Variables that remained in the final model were those with p-values <0.05 based on the Satterthwaite-adjusted F-statistic. We used SUDAAN Version 9.0 (Research Triangle Institute, Research Triangle Park, NC) for all analysis.

RESULTS

Overall CMV seroprevalence among women 20-49 years-old was 61.3% (95% CI: 58.9-63.6%) (Table 1). In univariate analysis, CMV seroprevalence was higher among women who were 30-39 and 40-49 years-old compared to 20-29 years-old. In age-standardized univariate analyses, CMV seroprevalence was higher among non-Hispanic Blacks and Mexican Americans than non-Hispanic Whites as well as higher among women born outside of the US, living below poverty, with less education, no health insurance, and high household crowding ($p<0.001$) (Table 1).

Overall age-standardized CMV seroprevalence was higher among women who had given birth to ≥1 child compared to women who had not, 66% vs. 49%, respectively ($p<0.001$) (Table 2). Similarly, CMV seroprevalence was significantly higher among women who had given birth to ≥1 child compared to women who had not given birth across all age and race/Hispanic origin groups (Table 2).

The multivariate logistic model included 2643 women with complete risk factor data. Higher CMV seroprevalence was independently associated with increasing number of live births, younger age at first sexual intercourse, ≥10 life time sexual partners and herpes type II-seropositivity, after controlling for age group, race/Hispanic origin, country of birth, living below poverty, and education level (Table 1). Considering number of live births as a continuous variable in the same multivariate logistic model, the adjusted odds ratio for each additional live birth was 1.2 (95%CI=1.1-1.3), with a significant trend (p-value<0.001).

DISCUSSION

In this population-based sample of U.S. women, increasing number of live births, early sexual debut, ≥10 life time sexual partners, and herpes type II seropositivity, were independently associated with higher CMV seroprevalence, after controlling for age and other sociodemographic risk factors. A previous study using data from the 1988-1994 NHANES found that sexual exposures were associated with higher CMV seroprevalence but did not assess the influence of parity [12]. Two studies among pregnant women found that increasing parity was independently associated with higher CMV seroprevalence, after controlling for age and sociodemographic risk factors, but sexual exposures were not included [13, 14]. We found that higher CMV seroprevalence was associated with having at least one live birth, overall and across all age and race/Hispanic groups. Approximately half of women who had not given birth remain susceptible to primary CMV infection, decreasing to approximately one third for women with ≥1 live birth.

Parents with a child shedding CMV and child care workers have annual CMV seroconversion rates that are much higher (3 to 12-fold) than those of parents with a child not shedding CMV [4]. CMV infection early in life can result from mother-to-infant

transmission through exposure to CMV in genital secretions during labor or in breastmilk or saliva. Additionally, close contact among children in the household or day care settings can result in horizontal transmission from child to child. Since young CMV-seropositive children may shed virus in body fluids for months after primary infection [15], the risk-period for CMV transmission from child to mother could coincide with a subsequent pregnancy. The risk of CMV seroconversion among women has been shown to increase over time throughout successive pregnancies [16]. The highest risk of congenital CMV infection in a study of infants born to mothers who seroconverted between deliveries was associated with an interval of <24 months between deliveries [17]. Data on interval between pregnancies and birth order for newborns with congenital CMV infection identified through population-based screening studies might be helpful to identify groups at highest risk.

Congenital CMV infection is also an important concern for women who are already seropositive when they become pregnant [17]. A study in the U.S. found a 10% annualized rate of reinfection among CMV seropositive women [18]. In populations with high maternal CMV seroprevalence, reinfection with a new CMV strain was a risk factor for delivering an infant with congenital CMV infection. In a study in Brazil, the annualized rate of reinfection among women delivering an infant with congenital CMV infection was 35% compared to 9% among women delivering uninfected infants [19]. Although the rate of mother-to-fetus transmission from non-primary infections is lower than with primary infection [2], non-primary maternal infections are estimated to account for the majority of congenital CMV infections [20-22] and CMV-related hearing loss [22]. Risk factors for CMV reinfection and reactivation are not well understood.

Our study had some limitations. Because NHANES is a cross-sectional study, we could not determine when seroconversion occurred. We used parity as a proxy to exposure to young children but data on general or occupational exposures to children were not available. We did not include women <20 years of age in the analysis because we did not have complete data on sexual exposures.

Routine serologic screening for CMV infection during pregnancy is not currently recommended in the United States [23]. Maternal IgM screening has limitations in differentiating primary from non-primary infections and IgG avidity tests are not widely available commercially [3, 23]. In addition, pre-conceptional immunity does not completely eliminate the risk of congenital CMV infection, effective treatments to prevent fetal infection are lacking, and the data on effectiveness of hygiene interventions targeted at pregnant women to reduce the risk of congenital CMV infection are limited [23]. We observed higher susceptibility to primary CMV infection among women <30 years who had not given birth. CMV seroprevalence remained fairly constant between 1988-1994 and 1999-2004 [9], whereas fertility rates among U.S. women <25 years-old has shown a substantial decline over the last decades [24]. A better understanding of the impact of declining fertility rates among younger women on the prevalence of congenital CMV infection is needed. The data we present can be modeled to assess secular trends in the prevalence of congenital CMV infection and produce more robust estimates of congenital CMV infection resulting from primary and non-primary maternal infection. This, in turn, would be useful for assessing the impact of interventions that might be implemented in the future.

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Synopsis

Parity and sexual exposures are independently associated with higher CMV seroprevalence among U.S. women of reproductive age, after controlling for age and sociodemographic risk factors.

Table 1

Age-adjusted CMV seroprevalence among women 20-49 years-old by sociodemographics, parity and sexual history, NHANES 1999-2004

Characteristic	Number (%) of women		Age-adjusted CMV IgG Seroprevalence % (95% CI)	Adjusted odds ratio (95% CI)[a]	P-value for beta in the logistic regression model
	Examined	Tested for CMV IgG			
Overall	4042	3710 (91.8)	61.3 (58.9-63.6)		
Age group (years)					
20-29	1502	1357 (90.3)	52.5 (48.9-56.1)	Ref	
30-39	1343	1242 (92.6)	64.2 (60.3-67.9)[b]	1.9 (1.5-2.5)	<0.001
40-49	1197	1111 (92.8)	66.0 (61.8-69.9)[b]	1.9 (1.3-2.8)	<0.001
Race/Hispanic origin					
Non-Hispanic White	1791	1654 (92.4)	48.6 (45.9-51.3)	Ref	
Non-Hispanic Black	861	776 (90.1)	87.1 (84.2-89.6)[b]	4.8 (3.5-6.7)	<0.001
Mexican American	1006	932 (92.6)	87.6 (84.2-90.5)[b]	4.4 (3.0-6.5)	<0.001
Other	384	348 (90.6)	83.1 (76.5-88.4)		
Country of birth					
U.S.	3031	2790 (92.1)	55.8 (53.2-58.4)	Ref	
Non-U.S.	1011	920 (91.0)	90.2 (86.4-93.3)[b]	2.9 (1.6-5.3)	<0.001
Family income to poverty ratio					
Below poverty threshold	866	795 (91.9)	78.7 (74.1-82.8)[b]	1.7 (1.1-2.5)	0.010
At or above poverty threshold	2857	2648 (92.7)	57.0 (54.2-59.7)	Ref	
Education level					
Below high school	1037	935 (90.2)	84.6 (80.9-87.8)[b]	2.2 (1.5-3.4)	<0.001
High school	935	854 (91.3)	66.0 (61.5-70.3)[b]	1.6 (1.2-2.1)	<0.003
Above high school	2066	1917 (92.8)	52.9 (49.6-56.1)	Ref	
Household crowding index					
High	965	903 (93.6)	85.6 (82.1-88.7)[b]	-	0.074[c]
Average	1963	1800 (91.7)	61.2 (58.5-63.9)[b]	-	0.356[c]
Low	1067	974 (91.3)	50.0 (45.9-54.1)	Ref	
Health insurance status					
Any insurance	3031	2786 (91.9)	57.6 (55.1-60.0)	-	0.151[c]
No insurance	963	889 (92.4)	75.3 (70.6-79.7)[b]	Ref	
Number of live births					
0	775	715 (92.3)	49.0 (44.4-53.7)	Ref	
1	761	709 (93.2)	60.1 (54.6-65.3)	1.3 (1.0-1.8)	0.101
2	905	860 (95.0)	64.8 (60.8-68.6)	1.6 (1.1-2.3)	0.011
3	604	567 (93.9)	74.5 (69.1-79.3)	1.9 (1.3-2.8)	0.003
4	228	215 (94.3)	78.2 (64.0-88.7)	2.0 (1.1-3.6)	0.026
≥5	161	153 (95.0)	83.8 (62.5-95.7)[d]	2.5 (0.8-7.5)[e]	0.100

Characteristic	Number (%) of women		Age-adjusted CMV IgG Seroprevalence % (95% CI)	Adjusted odds ratio (95% CI)[a]	P-value for beta in the logistic regression model
	Examined	Tested for CMV IgG			
Age at first sexual intercourse					
<18 years	1963	1838 (93.6)	64.4 (61.4-67.3)[b]	1.3 (1.1-1.6)	0.017
≥18 years	1568	1459 (93.1)	55.7 (52.2-59.1)	Ref	
Number of life time sexual partners					
0-9	2764	2579 (93.3)	58.2 (55.5-60.9)	Ref	
≥10	742	696 (93.8)	66.3 (62.3-70.2)[b]	1.4 (1.1-1.9)	0.012
Herpes type II serology					
Positive	1057	1049 (99.2)	76.6 (73.7-79.3) [b]	1.9 (1.5-2.6)	<0.001
Negative	2658	2608 (98.2)	55.2 (52.3-58.1)	Ref	
History of sexually transmitted disease					
Any	388	365 (94.1)	67.8 (61.0-74.1)[f]	-	0.527[c]
None	3144	2935 (93.4)	59.5 (56.9-62.1)	Ref	
Oral contraceptive use					
Any	2693	2532 (94.1)	59.2 (56.4-61.9)[f]	-	0.852[c]
None	902	823 (91.2)	66.7 (61.2-71.8)	Ref	

[a]Adjusted odds ratios obtained from the final logistic regression model (n=2643) that included age group, race/Hispanic origin, country of birth, family income to poverty ratio, education level, number of live births, age of first sexual intercourse, number of life time sexual partners and herpes type II serology. Group representing 'other' race/Hispanic origin not included in the logistic regression model.

[b]P-value <0.001 from univariate analysis comparing subgroup to reference group for each cofactor

[c]P-values for beta based on the full logistic regression model.

[d]Estimate considered unstable because relative standard error of percent negative was >30%

[e]P-value <0.001 for test of linear trend with increasing number of live births from 0-5 or more

[f]P-value <0.05 from univariate analysis comparing subgroup to reference group for each cofactor

Table 2

CMV seroprevalence among women 20-49 years-old by parity and age group or age-adjusted by race/Hispanic origin, NHANES 1999-2004

Characteristic	n, CMV Seroprevalence, % (95% CI)				P-value[a]
	Women who had given birth to ≥1 child		Women who had not given birth		
Overall	2503	66.0 (63.1-68.9)	715	49.0 (44.4-53.7)	<0.001
Age group					
20-29	685	62.5 (57.1-67.7)	426	40.7 (35.4-46.1)	<0.001
30-39	915	68.2 (63.5-72.7)	168	52.8 (43.5-62.0)	0.004
40-49	903	66.9 (62.2-71.3)	121	52.6 (42.7-62.3)	0.007
Race/Hispanic origin					
Non-Hispanic White	1058	52.6 (48.7-56.4)	386	39.2 (33.2-45.4)	<0.001
Non-Hispanic Black	544	90.1 (87.2-92.5)	123	74.5 (63.9-83.3)	0.002
Mexican American	691	91.2 (88.2-93.6)	120	71.4 (58.4-82.2)	0.001

[a]P-value from t-test comparing women who have given birth at least once to those who have never given birth