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Seroepidemiological Survey of Cytomegalovirus Infection among Pregnant Women in Sudan

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Abstract

Human Cytomegalovirus (HCMV) is a leading healthcare problem associated with stillbirth and congenital abnormalities. Determining the seroprevalence and the possible risk factors related to HCMV infections may be a cornerstone in preventing its complications. This cross-sectional study was conducted in Kassala and River Nile States to determine the seroprevalence and risk factors associated with HCMV infection in pregnant women. One hundred eighty-four (n = 184) blood specimens were collected from pregnant women from February 2018 to January 2020. Enzyme-linked immunosorbent assay (ELISA) was used to detect HCMV-specific IgG and IgM antibodies. Socio-demographical characteristics of the women were collected using structured questionnaires. The results showed that HCMV IgG was detected in 170 (92.4%) of the blood specimens, and IgM was detected in 29/93 (31.2%). There was a significant relationship between the history of miscarriage and the presence of IgG and IgM with a p-value = 0.001 and between HCMV IgM and gestational stage (p-value = 0.028). The study found a strikingly high seroprevalence of HCMV infections among pregnant women in the investigated States. This high percentage of illiterate housewives living in rural areas makes it possible to reduce the incidence of HCMV infection in pregnant women by improving their knowledge, attitude, and practice regarding the route of viral transmission, which may reflect in lowering the rate of congenital diseases in their infants.

Keywords: Pregnant Women, HCMV, IgG, IgM, River Nile State, Kassala State

Introduction

The human Cytomegalovirus (HCMV) or human herpesvirus 5 is one of the leading causes of congenital infections. Pregnant women can be infected with HCMV by a primary disease, reactivation, or reinfection of a different HCMV strain during pregnancy (De Paschale et al. 2009; van Zuylen et al. 2014; Alvarado-Esquivel et al. 2018). HCMV has different genotypes based on glycoproteins in the envelope (gB (*UL55*) and gH (*UL75*)), which might influence the severity of diseases (de Vries et al. 2013; Alwan et al. 2019). For instance, gB1 and gB2 genotypes are linked to hepatosplenomegaly and hearing impairment. Also,

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the gB2 genotype was connected to an abnormality in the image of ultrasound and/or magnetic resonance in fetuses and newborns congenitally infected, unlike gB4, which might not reveal an abnormal image (Novak et al. 2008; Brañas et al. 2015).

HCMV has different spreading routes that directly contribute to its high prevalence; these can be via body fluids like saliva, breastfeeding, sexual contact, and placental transfer or through organ transplantation, including blood transfusion, solid-organ transplant, or hematopoietic stem cell transplantation. Moreover, due to the lack of a specific drug for HCMV infection and no vaccine, along with the less knowledge about congenital HCMV in health care and the public, besides, asymptomatic infection in newborns, so they will not be defined at birth, all these factors significantly contributed to the magnitude of HCMV infection as a great health problem (Shedlock et al. 2012; Manicklal et al. 2013; Alwan et al. 2019).

HCMV viral transmissions occur among all age groups, races, and socioeconomic classes throughout the modernised and developing parts of the world (Emmanuel and Ogbu 2017). HCMV seroprevalence ranges from 40 % and may reach up to 100%, especially in high-risk populations like HIV-infected patients and those on immunosuppressive treatment (Delvincourt et al. 2014).

Feto-maternal transmission can occur during pregnancy through the placenta, during delivery through direct contact with maternal cervical secretions and blood, and postnatal via breast milk (Bhide and Papageorghiou 2008). Strikingly, transplacental transmission can occur even in women with pre-existing seroimmunity to CMV, which can be explained either by viral reactivation or infection with a new, different strain of CMV (reinfection) during the pregnancy (Hassan et al. 2014).

Infants infected with the virus can present many symptoms and signs, from petechial rash, jaundice, and hepatosplenomegaly to more severe manifestations, including neurologic abnormalities such as microcephaly and lethargy. Also, chorioretinitis and optic atrophy occur in approximately 10% of symptomatic infants (Boppana et al. 2013). Vertical transmission of the virus during primary HCMV infection is about 30–35%, while for secondary infection and reactivation, it is in the range of 1.1–1.7%, which is a significantly lower transmission rate (Marsico and Kimberlin 2017).

CMV among congenitally-infected infants can cause permanent morbidities such as deafness, blindness, and mental retardation (Kenneson and Cannon 2007; Yinon et al. 2010; Simonazzi et al. 2017). In addition, HCMV infection during pregnancy is the most common congenital infection worldwide, with an estimated incidence of approximately 0.6 to 0.7% of all live births in the developed world. The prevalence of congenital HCMV infection in developing countries significantly varies within and between countries, ranging from 0.6 to 6.1% of all live births (Lanzieri et al. 2014; Marsico and Kimberlin 2017).

Sudan is one of the developing countries and consists of 18 states. Out of 91 pregnant women, 67 (73.6%) were HCMV IgG positive in the Khartoum State, a capital city (Ali 2016). In Western Sudan, out of 231 pregnant women, 167 (72.2%) were HCMV IgG positive (Hamdan et al. 2011). However, there need to be more documentation systems to monitor the seroprevalence of HCMV in the other region of Sudan. Therefore, this study was conducted to screen the seroprevalence of HCMV IgG and IgM antibodies among pregnant women in the Kassala State and River Nile State and to correlate possible risk factors, including age, educational level, past miscarriages, gestational stage of pregnancy, and place of residence. This study will help understand the possible transmission risk factors and preventive measures.

Experimental

Materials and Methods

Study area, duration, and population. The study was conducted in the Kassala State in Eastern Sudan, where Kassala is the capital city, and the River Nile State in North Sudan, where El Damer is the capital. The study was a descriptive cross-sectional study conducted on pregnant women with or without a history of miscarriage attending the Al-Saudi Hospital in the Kassala State and the El Damer Teaching Hospital between February 2018 and January 2020.

Sample size, sampling technique, and data collection. For this study, one hundred eighty-fou (n = 184) pregnant women were collected by convenience sampling technique. Socio-demographic characteristics of the women were collected using structured questionnaires that included information on age, gestational trimester, past miscarriages, education levels, occupation, and place of residence.

Detection of CMV IgG and IgM with ELISA. Five ml of whole blood samples were collected from each participant by vein puncture into a container of ethylene diamine tetraacetic acid (EDTA) as an anticoagulant. Then, each blood specimen was centrifuged at 3,000 rpm for 5 minutes to obtain the plasma. It was placed into a standard container and stored at –20°C until analysed. Specimens were analyzed using a commercially available enzyme-linked immunosorbent assay (CMV IgG and CMV IgM ELISA Kits) (Fortress Diagnostics Limited, UK) for the qualitative detection of the specific CMV IgG and IgM antibodies, following the manufacturer's instructions.

Table I
Socio-demographic characteristics of pregnant women enrolled in this study (n = 184).

Variables		Frequency	Percentage
Age group/years	15–24	70	38%
	25–34	83	45.1%
	35–44	31	16.9%
History of miscarriage	Yes	87	47.3%
	No	97	52.7%
Gestational stage	First	61	33.2%
	Second	58	31.5%
	Third	65	35.3%
Occupation	Housewife	184	100%
	Employee	0	0%
Residence	Urban	93	50.5%
	Rural	91	49.5%
Educational level	Illiterate	100	54.4%
	Primary	26	14.1%
	Secondary	44	23.9%
	Graduated	14	7.6%

Statistical analysis. Data were analysed by a Statistical Package for the Social Sciences (SPSS) software programme version 20.0 (IBM, USA). The Chi-square test was applied to find an association between seroprevalence and socio-demographic variables, with the statistical significance difference set at $p \leq 0.05$.

Results

Socio-demographic data of the studied population. A total of one hundred eighty-four blood specimens (n = 184) were collected from pregnant women in the AL-Saudi Hospital in the Kassala State (n = 91) and the El Damer Teaching Hospital in the River Nile State (n = 93). All pregnant women were housewives. The socio-demographic characteristics of all participants are shown in Table I. The participating women of different ages ranged from 15 to 44 years, had a mean age of 29.5 ± 3.5.

The specimens collected from the River Nile State were tested for CMV IgG and IgM antibodies using ELISA kits. In the 93 blood samples that were tested, 81/93 (87.1%) specimens were positive for CMV IgG, while 29 (21.2%) were positive for CMV IgM (Table II and III). There was a significant relationship between the history of miscarriage and the presence of IgG and IgM with a *p*-value equal to 0.001 and between CMV IgM and gestational stage with a *p*-value equal to 0.028 (Table II and III). All participants from the River Nile State lived in urban places. While for pregnant women attending the Al-Saudi Hospital in the Kassala State, the age group starts from 15 years because it is a rural area and the marriage age is very young. Eighty-nine women (97.8%) were positive for CMV IgG, and two (2.2%) were negative. All participating pregnant women were housewives, living in rural places, and illiterate (Table IV).

Table II
Association between CMV (IgG) and socio-demographic data of pregnant women in the El Damer teaching hospital (n = 93).

Variables		Total	CMV (IgG)		*p*-value
			Positive (%)	Negative (%)	
Age group/years	20–30	69	62 (89.9)	7 (10.1)	0.18
	31–40	24	19 (79.2)	5 (20.8)	
History of miscarriage	Yes	58	56 (96.6)	2 (3.4)	0.001
	No	35	25 (71.4)	10 (28.6)	
Gestational stage	First	37	30 (81.1)	7 (18.9)	037
	Second	33	30 (90.9)	3 (9.1)	
	Third	23	21 (91.3)	2 (8.7)	
Occupation	Housewife	93	81 (87.1)	12 (12.9)	–
	Employee	0	0 (0)	0 (0)	
Residence	Urban	93	81 (87.1)	12 (12.9)	–
	Rural	0	0 (0)	0 (0)	
Educational level	Primary	26	24 (92.3)	2 (7.7)	0.38
	Secondary	44	36 (81.8)	8 (18.2)	
	Graduated	14	12 (85.7)	2 (14.3)	
	Illiterate	9	9 (100)	0 (0)	

Chi-square test at $p \leq 0.05$

Table III
Association between CMV (IgM) and socio-demographic data of pregnant women in the El Damer teaching hospital (n = 93).

Variables		Total	CMV (IgG)		*p*-value
			Positive (%)	Negative (%)	
Age group/years	20–30	69	22 (31.9)	47 (68.1)	0.80
	31–40	24	7 (29.2)	17 (70.8)	
History of miscarriage	Yes	58	28 (48.3)	30 (51.7)	0.001
	No	35	1 (2.9)	34 (97.1)	
Gestational stage	First	37	8 (21.6)	29 (78.4)	0.028
	Second	33	16 (48.5)	17(51.5)	
	Third	23	5 (21.7)	18(78.3)	
Occupation	Housewife	93	29 (31.2)	64 (68.8)	–
	Employee	0	0 (0%)	0 (0)	
Residence	Urban	93	29 (31.2)	64 (68.8)	–
	Rural	0	0 (0)	0 (0)	
Educational level	Primary	26	12 (46.2)	14 (53.8)	0.14
	Secondary	44	10 (22.7)	34 (77.3)	
	Graduated	14	3 (21.4)	11 (78.6)	
	Illiterate	9	4 (44.4%)	5 (55.6)	

Chi-square test at $p \leq 0.05$

Table IV
Association between CMV (IgG) and socio-demographic data of pregnant women in the Al-Saudi Hospital in the Kassala State (n = 91).

Variables	Total (n = 91)	CMV IgG result		*p*-value
		Positive (n = 89)	Negative (n = 2)	
Age group				
15–24	35	33 (94.3%)	2 (5.7%)	0.195
25–34	37	37 (100%)	0 (0.0%)	
35–44	19	19 (100%)	0 (0.0%)	
History of miscarriage				
Yes	29	29 (100%)	0 (0.0%)	0.328
No	62	60 (96.8%)	2 (3.2%)	
Pregnancy trimester				
First trimester	24	23 (95.8%)	1 (4.2%)	0.606
Second trimester	25	25 (100%)	0 (0.0%)	
Third trimester	42	41 (97.6%)	1 (2.4%)	
Occupation				
Housewife	91	89 (97.8%)	2 (2.2%)	–
Employee	0			
Residence				
Urban	0			–
Rural	91	89 (97.8%)	2 (2.2%	
Education level				
Illiterate	91	89 (97.8%)	2 (2.2%)	–
Primary	0			
Secondary	0			
Graduation	0			

Chi-square test at $p \leq 0.05$

Discussion

Human cytomegalovirus (HCMV) is the most common cause of congenitally acquired infections. The present study aimed to detect HCMV antibodies in pregnant women in the River Nile State, located in the Eastern North and the Kassala State, one of the rural areas in Eastern Sudan, where daily hygiene status is inadequate. Among 184 blood specimens tested for HCMV IgG, 170 (92.4%) were positive, in line with previous reports that rural residents are 92% seropositive for the virus (Hassan et al. 2014). This high percentage of seroprevalence was slightly lower than the result obtained in Nigeria, where 97.2% of participants were CMV IgG positive (Akinbami et al. 2011), Northern Turkey – 97.3% (Uyar et al. 2008), Palestine – 96.6% (Neirukh et al. 2013), and in Asir Region, Kingdom of Saudi Arabia the seroprevalence was 95.7–100% (Almaghrabi et al. 2019). These seroprevalence results differ slightly from that recorded for the central Mexican city of Aguascalientes, where it was 89.6% (Alvarado-Esquivel et al. 2018). This discrepancy may be attributed to the different endemicity of CMV infections in these countries (Lantos et al. 2017; Udeze et al. 2018).

Interestingly, there was a different percentage of seroprevalence of HCMV in pregnant women within Sudanese States. A similar study was conducted in Khartoum State and found that out of 91 pregnant women, 67 (73.6%) were CMV IgG positive (Ali 2016). Another study in Western Sudan to estimate the seroprevalence of HCMV in pregnant women demonstrated that out of 231 pregnant women, 167 (72.2%) were CMV IgG positive (Hamdan et al. 2011). Socioeconomic status and ethnicity explain these differences within a country (van Zuylen et al. 2014).

When analyze the results by the gestational trimester, the positive percentage of IgM in the first trimester was 8 (21.6%). Primary HCMV infection is critical because it is a significant risk factor for vertical transmission of HCMV infection to newborns (Umeh et al. 2015). The prevalence of congenital CMV transmission rates is 50% when primary CMV infection occurs in pregnant women and less than 2% in non-primary infection of pregnant women (Davis et al. 2017). Moreover, HCMV causes congenital malformations and miscarriages when it is a primary infection during the first trimester. The risk of developing fetal manifestations of the disease is more significant when the primary infection occurs during the first thirteen weeks of pregnancy (De Paschale et al. 2009).

In this study, the women from the River Nile State who had a history of miscarriage screened positive for HCMV IgG and IgM and were significantly associated with HCMV infection ($p \leq 0.05$). These findings may indicate that HCMV could be one of the significant risk factors for miscarriage among pregnant women in Sudan. Illiteracy and low education levels are associated with an increased likelihood of contracting HCMV through direct contact with infectious secretions from their children and poor hygienic conditions in their homes. Low socioeconomic status also contributes significantly to acquiring HCMV infection (Hassan et al. 2014).

In comparing the two States, the results indicated that the prevalence of CMV IgG in the River Nile State was lower than in the Kassala State. This study also documented that the prevalence of HCMV infection in Sudan varies across states; this difference might be due to lifestyle because in the Kassala State, all participants live in rural areas and are not educated. Also, these differences were due to socioeconomic status and ethnicity within the country (van Zuylen et al. 2014).

HCMV infection during pregnancy is associated with severe neurologic deficits in newborns, infants, and immunocompromised individuals (Zhang and Fang 2019). It is, therefore, necessary to prevent the disease rather than treat it. We can do prevention by screening blood to avoid CMV transmission (Emmanuel and Ogbu 2017). In addition, there is an urgent need for increasing awareness in society that infectious body fluids such as saliva and urine of infected children are an essential source of HCMV infection during pregnancy. Also, promoting preventive attitudes and practices (i.e., washing hands whenever they come into contact with a child's saliva or urine, not sharing drinking glasses or eating utensils with infants, and not kissing infants on the mouth or cheek) will be generally acceptable and effective measurements (Lazzarotto et al. 2011). Therefore, pregnant women must be protected from HCMV infection through proper hygiene and behavior; pregnant women must be educated about the consequences of acquiring HCMV infection; routine screening for HCMV infection should be performed during pregnancy in the obstetric unit. Moreover, antiviral prophylaxis should be given to reduce the risk of HCMV infection. In addition, recent studies have shown that the administration of hyper immunoglobulin (CMV HIG) to pregnant women exposed to CMV significantly reduces the rate of vertical CMV transmission and improves neonatal outcomes (van Zuylen et al. 2014).

Conclusions

This study demonstrated a higher seroprevalence rate of HCMV among pregnant women in the Kassala State (rural) than in the River Nile State (urban). The high percentage of illiterate women living in rural areas makes it possible to reduce the incidence of HCMV infection in pregnant women by improving their

knowledge, behavior, and practice regarding the virus's transmission route, which may translate into lower rates of congenital diseases in their infants.

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Availability of data and material

All data generated or analyzed during this study are included in this published article.

Ethical statement

Ethical approval for this study was obtained from the Institutional Ethics Committee, Deanship of Scientific Research, Sudan University of Science and Technology, which ensured that all ethical considerations for the research were followed in a manner that protected patient confidentiality and privacy. Informed consent was obtained from all participants. Participant privacy and confidentiality were maintained for all samples. Permission was obtained from the hospitals.

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Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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