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■ Original Research Article

Cytomegalovirus Infection Among Women with Recurrent Miscarriages

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ABSTRACT

BACKGROUND: The foetal consequences of Cytomegalovirus (CMV) infection have made it one of the most serious infections contracted during pregnancy. Recurrent pregnancy loss (RPL)/recurrent miscarriage (RM) is a challenging problem for the Obstetrician. Human cytomegalovirus is a major cause of congenital infection and has been implicated as a cause of pregnancy loss. Knowledge about the magnitude of this problem in our locality will help in developing methods of prevention of this infection and prompt treatment of infection will improve obstetric outcome.

OBJECTIVE: To determine the prevalence of CMV infection among women with recurrent pregnancy loss, establish if there is an association between CMV infection and recurrent pregnancy loss and assess the level of awareness of CMV.

METHODOLOGY: This was a multi centred cross-sectional study involving 42 pregnant women presenting with recurrent miscarriage and 42 postnatal women with no previous history of miscarriages or poor obstetric outcome. Interviewer-administered questionnaire was used to obtain socio-demographic information which included age,

socioeconomic class, parity and gestational age at present pregnancy loss. Blood samples were collected from the respondents and cytomegalovirus antibodies (IgG and IgM) were assayed for in both groups. Data was analysed using Statistical Package for Social Sciences version 22.

RESULTS/CONCLUSION: The seroprevalence of CMV IgG among women with recurrent miscarriage and normal women was 85.7% and 76.2% respectively. There was no significant association between CMV infection and recurrent miscarriage (p =0.405 and 0.676 for IgG and IgM respectively). The level of awareness of the respondents about CMV was low (4.8%).

CONCLUSION: This study suggests that due to the high seroprevalence of CMV and the low level of awareness of CMV infection among the respondents, all pregnant women should be educated about CMV and the methods of prevention of CMV infection. Patients with recurrent miscarriage should also be counselled about CMV.

KEY WORDS: Recurrent Pregnancy loss, cytomegalovirus, cytomegalovirus antibody, immunoglobulin G(IgG), immunoglobulin M(IgM).

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INTRODUCTION

Human cytomegalovirus (CMV) is a member of the family Herpesviridae and belong to the subfamily beta Herpesviridae. It has worldwide distribution and infects humans of all ages and socioeconomic group, with no seasonal or epidemic patterns of transmission.[1] The common modes of infection with CMV are through saliva, urine, stool, breast milk, unscreened blood transfusion, cervical secretions, and semen. For most healthy people who acquire CMV infection after birth or through blood transfusion, there are few symptoms and no long term sequelae.[2,3] The major risk factor for maternal acquisition of CMV during pregnancy is frequent and prolonged contact with a child less than three years of age.[4,5] This occurs among women with a child in the home or among women employed in child care centres or schools.[6,7] Another group of high risk women are those who are seronegative young and poor.[5] Other high risk groups include unborn babies whose mothers become infected with CMV during pregnancy and children or adults whose immune systems have been weakened by disease or drug treatment such as organ transplant recipients or people infected with HIV.[8]

Spontaneous pregnancy loss is a frustrating experience and can be physically and emotionally tasking for couples especially when faced with recurrent losses.[2] Embryo-foetal infections like CMV have been reported to cause recurrent pregnancy loss (recurrent miscarriage).[9] The proposed mechanisms include direct infection of the foetus or the placenta, placental insufficiency, endometritis, endocervicitis, chorioamnionitis and altered immune response.[9] Available reports on the role of CMV infection in recurrent pregnancy loss shows conflicting results. Some studies showed higher prevalence while others showed comparable and even less prevalence of antibodies to CMV among women with recurrent pregnancy loss compared to normal pregnant women.[2]

The objectives of this study were to determine the prevalence of CMV infection among patients with recurrent pregnancy loss, to ascertain if there is a significant association between CMV infection and recurrent pregnancy loss and assess the level of awareness about CMV infection in our environment.

MATERIALS AND METHODS

This was a multi centred cross-sectional study in which respondents were recruited from the Jos University Teaching Hospital, Plateau State Specialist Hospital and Faith Alive Hospital. The Jos University Teaching Hospital (JUTH) is a 600-bed tertiary health institution located in Jos, the capital of Plateau State in North-Central Nigeria. The department has a gynaecological emergency unit, among other service points, which offers gynaecological emergency services to patients from Plateau state and receives referrals from neighbouring states including Bauchi, Benue, Kogi, Gombe, Nasarawa, Adamawa, Taraba and parts of Kaduna and Niger states.

Plateau State Specialist Hospital is a 150–bed specialist hospital located within Jos metropolis with a well-established department of Obstetrics and Gynaecology. Referrals are received from the general hospitals and primary health clinics from every part of the state.

Faith Alive Hospital is a non-profit, non-governmental hospital that offers PMTCT services to the general populace. The hospital offers Obstetrics and Gynaecology services usually provided by Consultants and Residents in Obstetrics and Gynaecology.

The study participants were women presenting with recurrent pregnancy loss (that is, the 3rd or more consecutive spontaneous pregnancy loss) at the gynaecological emergency and gynaecological wards of the Jos University Teaching Hospital (JUTH), Plateau State Specialist Hospital and Faith Alive Hospital, Jos-Nigeria. The second group recruited were women presenting at the postnatal clinic with no prior history of miscarriage or poor obstetric outcome. Forty-two women with recurrent miscarriage and forty-two healthy age-matched postnatal women were recruited for the study over a period of fifteen months, from November 2016 to January 2018. A questionnaire was administered to each participant and serial numbers assigned. The information that was collected included demographics, parity, gestational age, obstetric history, gestational age at pregnancy loss and number of pregnancy losses. Awareness about CMV was sought and knowledge on possible ways of acquiring and preventing the infection were asked. Blood samples were collected for cytomegalovirus antibody screening for all participants. The sample bottles were assigned serial numbers to match the patients. The patients' phone numbers were collected to enable the researcher follow up with results.

All statistical analysis were performed using SPSS software version 22.

Approval for the study was obtained from the Ethical Committees of the Jos University Teaching Hospital (JUTH), Plateau State Specialist Hospital and Faith Alive Hospital, Jos.

The nature, aim and objectives of the study were explained to each woman and written consent obtained before recruitment into the study. The participants were assured of confidentiality of their information. The women were offered the option to opt out of the study, bearing in mind such action would not in any way compromise the quality of care they would receive at any service point.

RESULTS

84 women were recruited for the study out of which 42 women had recurrent miscarriage and 42 were normal postnatal women.

Table 2: CMV infection among the participants

CMV infection	Study Group		Total n=84	*P**
	Recurrent miscarriage n=42	Normal postnatal women n=42		
IgG Positive	36(85.7)	32(76.2)	68(81.0)	
Negative	6(14.3)	10(23.8)	16(19.0)	0.405
IgM Positive	4(9.5)	2(4.8)	6(7.1)	
Negative	38(90.5)	40(95.2)	78(92.9)	0.676

*Fishers derived P-value

Table 1: Background characteristics of study Participants

Characteristics	Study group		Total n=84(%)	*P**
	Recurrent miscarriage n=42(%)	Normal postnatal women n=42(%)		
Age (years)				
<35	31(73.8)	26(61.9)	57(67.9)	
35+	11(26.2)	16(38.1)	27(32.1)	0.350
Education				
Non formal	7(16.7)	2(4.8)	9(10.7)	
Primary	3(7.1)	7(16.7)	10(11.9)	
secondary	10(23.8)	20(47.6)	30(35.7)	
Tertiary	22(52.4)	13(31.0)	35(41.7)	0.018
Occupation				
Housewife	15(35.7)	17(40.5)	32(38.1)	
Trading	9(21.4)	8(19.1)	17(20.2)	
Teaching	7(16.7)	3(7.1)	10(11.9)	
Others	11(26.2)	14(33.3)	25(29.8)	0.558
Parity				
0	11(26.2)	0(0.0)	11(13.1)	
1-4	30(71.4)	37(88.1)	67(79.8)	
>4	1(2.4)	5(11.9)	6(7.1)	<0.001

*Fishers derived P-value

Table 1 shows a comparison of demographic characteristics of the participants in the two study groups. The overall mean age was 32.11±5.98 years. More women with recurrent miscarriage had tertiary education [22(52.4%)]. The past obstetric history of the participants with recurrent miscarriage is shown in figure 1. Thirty (71.4%) have had normal deliveries in the past while 5(11.9%) have had intrauterine fetal death. Table 2 shows the distribution of the CMV serostatus of the participants.

The overall prevalence of CMV using IgG was 81.0%. The prevalence of CMV among women with recurrent miscarriage was 85.7% and 76.2% among normal postnatal women. Four women with recurrent miscarriage (9.5%) were seropositive for CMV IgM compared to 2(4.8%) among the normal postnatal women. However, these differences were not statistically significant.

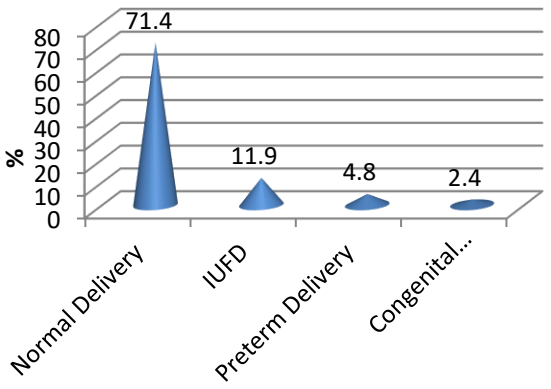

Figure1: Past obstetric history of the women with recurrent miscarriage

Various combinations of CMV IgG and IgM serostatus among the participants were shown in table 3. No respondent was seropositive for only CMV IgM. Table 4 shows that 33(78.6%) of the participants with recurrent miscarriages had 3 pregnancy losses.

Table 5 shows that only 4(4.8%) of the participants were aware of cytomegalovirus. There was no significant association between awareness of CMV infection and recurrent miscarriage (P > 0.05). Knowledge about mode of transmission, complications, and methods of prevention of CMV infection is low as shown in table 6. No respondent was aware that miscarriage could be a complication of CMV infection.

Table 3: Various combinations of the CMV ser status of the participants

CMV	Recurrent miscar-riage n=42	Normal postnatal women n=42	Total n=84	*P**
IgG(+)IgM(-)	32(76.2)	30(71.4)	62(73.8)	0.804
IgG(-)IgM(+)	0(0.0)	0(0.0)	0(0.0)	
IgG(+)IgM(+)	5(11.9)	2(4.8)	7(8.3)	0.433
IgG(-) IgM(-)	5(11.9)	10(23.8)	15(17.9)	0.254

*Fishers derived P-value

Table 4: Distribution of the number of pregnancy losses among the participants with recurrent miscarriag

CMV	Recurrent Miscarriage		Total n=42
	3	>3	
IgG			
Positive	29(69.0)	7(16.7)	36(85.7)
Negative	4(9.5)	2(4.8)	6(14.3)
IgM			
Positive	1(2.4)	3(7.1)	4(9.5)
Negative	32(76.2)	6(14.3)	38(90.5)

Table 5: Awareness about cytomegalovirus infection among the participants

Awareness	Study group		Total n=84(%)	*P**
	Recurrent miscar-riage n=42(%)	Normal postnatal women n=42(%)		
Yes	1(2.4)	3(7.1)	4(4.8)	
No	41(97.6)	39(92.9)	80(95.2)	>0.616

*Fishers derived P-value

Table 6. Knowledge about mode of transmission of CMV, susceptible group of people, complications of CMV infection and method of prevention of infection among participant

Characteristics	Study group		Total
	Recurrent miscarriage n=42(%)	Normal postnatal women n=42(%)	n=84(100%)
Mode of transmission			
Unprotected sexual inter-course	1(2.4)	1(2.4)	2(2.4)
Don't know	0(0.0)	2(4.8)	2(2.4)
Susceptibility			
Pregnant women	1(2.4)	1(2.4)	2(2.4)
Unborn babies	1(2.4)	1(2.4)	2(2.4)
Daycare workers	0(0.0)	1(2.4)	1(1.2)
Health care workers	0(0.0)	1(2.4)	1(1.2)
Complication			
IUFD	1(2.4)	0(0.0)	1(1.2)
Don't know	0(0.0)	3(7.1)	3(3.6)
Prevention			
Regular and thorough hand-washing	0(0.0)	1(2.4)	1(1.2)
Avoid kissing children on or near the mouth	0(0.0)	1(2.4)	1(1.2)
Avoid sharing towels or washcloths with your child	0(0.0)	1(2.4)	1(1.2)

DISCUSSION

The seroprevalence of anti-CMV IgG in women with recurrent miscarriage in this study was 85.7%. The implication of this high seroprevalence is that most of the patients that presented with recurrent miscarriage have been previously exposed to the virus. Bearing in mind the risk factors for CMV infection transmission, the possible reasons for this high seroprevalence may include low standard of hygiene in our environment, low socio-economic status and cultural practices that aid in the propagation of the infection. However, the presence of IgG makes it difficult to determine if seroconversion occurred during the recent miscarriage since the CMV serostatus of the women were unknown before conception. Although individuals that are CMV IgG positive are said to be `protected' or `immuned**,** it is worth noting that the presence of CMV IgG antibodies is not completely protective because an individual can be infected primarily with a different strain or have a reactivation of a latent virus. Thus, vertical transmission can still occur in pregnant women who are CMV IgG seropositive. The chances of transmission are however less than in women that seroconvert in pregnancy. The finding in this study is similar to the finding in the study carried out by Sherkat et al where the CMV IgG seroprevalence among women with recurrent miscarriage was 90.6%.[2] Similar findings were obtained in other studies: Kafi et al[10] found a seroprevalence of 97.8%, Odland et al[11] found a seroprevalence of 78% and Hammed et al[12] found a seroprevalence of 92.9% among women with recurrent pregnancy loss. The finding of a high seroprevalence of CMV IgG in patients with recurrent pregnancy loss in this study differs from the finding in a study done by Johnson et al where the seroprevalence rate for CMV IgG was 35%.[13] These different findings may be due to different study populations, variation in sample sizes and differences in the interpretation of the various diagnostic kits used to assay for CMV antibodies.

The seroprevalence of anti CMV IgM in patients with recurrent pregnancy loss in this study was 9.5%. This may suggest that these women had primary infection. The implication of a primary infection is that CMV may have been responsible for the pregnancy loss in these patients. However, the interpretation of a positive CMV IgM result can be problematic since CMV IgM persists in some individuals for one or more years following primary infection. The seroprevalence of CMV IgM in women with recurrent pregnancy loss obtained in this study is higher than that obtained in studies by Sherkat et al[2] and Ariani et al[14] who found CMV IgM seroprevalence to be 2.3% and 1.3% respectively. From the study by Kafi et al,[10]a higher CMV IgM seroprevalence (38.3%) was obtained for women presenting with pregnancy loss. Possible explanations for the differences include different study populations with varying socio-demographic characteristics, differences in the number of women recruited for the studies, the high false positive rate of the IgM CMV assay and variations in the interpretation of results of different kits.

The seroprevalence of CMV IgG in the normal postnatal women in this study was 76.2%. This is similar to the findings in studies by Odland et al (81.1%) [11] and Abdolreza et al (78%)[15] but higher than the seroprevalence obtained by Johnson et al (65%).[13] Numerous studies done in Nigeria among pregnant women showed very high values (94.8% in Kaduna,[8] 98.7% in Sokoto,[16] 84.2% in Bida [17] and 97.2% in Lagos[18]). The high seroprevalence in this study and other studies within the country could be due to: low socio-economic status, failure to adhere to simple hygienic practices like regular

handwashing, large family sizes of many homes in developing countries which ensures that frequent and prolonged contact with children less than 3 years of age will occur and counselling and screening for CMV is not done in our environment like in some developed countries (Spain, Israel, Netherlands, Portugal and Austria).[19,20]

About 4.8% of the normal postnatal women were seropositive for CMV IgM. This is like the findings in the study by Sherkat et al[2] which showed that 2.3% of the normal multiparous women were seropositive to CMV IgM. Emovon et al [21] conducted a study in Southern Nigeria and found that only 4% of normal pregnant women were positive for IgM which is like the finding in this study. The finding in this study is however not in keeping with a study by Hameed et al in which no control was found to be seropositive to CMV IgM.[12] The variations in the seroprevalences of IgM in different studies may be attributed to different sample sizes for various studies, the high false positive rate for IgM, differences in assay methods and time of collection of the blood samples. If an individual has a negative CMV IgM result, this does not completely rule out a primary infection with CMV. This is because the sample may have been collected too early in the course of the primary infection and IgM levels may have not reached detectable levels. The high false positive rate of CMV IgM may be attributed to cross-reactivity with autoimmune diseases and some viral infections like influenza, Epstein Barr virus, measles and Herpes Simplex.[22]

In this study, more women with recurrent miscarriage were seropositive for IgG and IgM compared to normal postnatal women's but these differences were not statistically significant (P=0.405 for IgG and P=0.676 for IgM). Therefore, there is insufficient evidence to associate CMV infection and recurrent miscarriage in this study. The implication of the finding in this study is that we cannot draw up a conclusion associating CMV and recurrent pregnancy loss. Radcliffe et al assessed CMV infection in women with recurrent miscarriage and found a significantly lower seroprevalence of CMV in women with recurrent miscarriage compared to their male partners and female controls.[23] Cook et al[24] used Polymerase Chain Reaction (PCR) to detect cytomegalovirus in gestational tissue of women with recurrent spontaneous abortions and none of the specimens contained evidence of CMV DNA. His finding suggested that CMV infection of gestational tissue is not a common direct cause of recurrent miscarriages.

The finding from this study is not in agreement with other studies that found significant association between CMV and recurrent miscarriage. Sherkat et al found that previous exposure to CMV significantly higher in patients with recurrent pregnancy loss than the control group.[2] Also, Kafi et al found significant association between CMV infection and frequency of abortion.[10]

Prevention remains the cornerstone of efforts to limit the burden of congenital CMV infection globally. Awareness about CMV infection is an important step in the prevention of CMV infection. In this study, only 4 (4.8%) of the participants knew about CMV. Possible reasons for this low level of awareness include: the respondents had never been educated about CMV by health care providers, the health care providers maybe do not appreciate the devastating effects of CMV infection in pregnancy or health messages about CMV are not usually given on the media. Emovon et al[21] in Nigeria also reported a low level of awareness (3%). Awareness is generally higher in developed countries (15% in Canada, 39% in Geneva, 34% in France).[25-27]

Two respondents were aware that pregnant women are susceptible to CMV infection. No respondent was aware that miscarriage is a possible complication of CMV infection and only one respondent knew that a method of prevention of CMV infection was by regular and thorough handwashing. In the study by William et al,[26] 74.6% of the women that were aware of CMV answered correctly to more than five preventive measures. This clearly shows that knowledge about CMV is lacking in our environment. Therefore, there is need for health education about CMV and methods of preventing infection among susceptible women. Since the level of awareness about CMV and methods ofpreventing infection is very low, the high seroprevalence of CMV IgG among the participants in this study is not surprising. Thus, the effects of CMV infection in pregnancy and the methods of prevention of the infection should be incorporated into the health talk given to pregnant women during antenatal clinic visits.

CONCLUSION

Significant association between CMV infection and recurrent pregnancy loss was not established from this study. However, the high seroprevalence of CMV suggests that many women have been exposed to this virus. Due to the high prevalence of CMV and low level of awareness among women from this study, pregnant women should be educated about the effects of CMV infection in pregnancy and the methods of prevention of the infection should be incorporated into the health talk given during antenatal clinic visits.

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