

ASSOCIATION OF SEROPOSITIVITY FOR CMV IGM AND IGG WITH ADVERSE PREGNANCY OUTCOME

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ABSTRACT

Objective: To find out the prevalence of antibodies against cytomegalovirus and their association with adverse pregnancy outcome in women, at Isra University Hospital Hyderabad.

Study Design: Cross-sectional study.

Place and Duration of Study: Department of Gynaecology & Obstetrics, Isra University Hospital (IUH) Hyderabad, from Jan to Jun 2018.

Methodology: Cytomegalovirus IgM and IgG antibodies in 305 women of reproductive age group were measured using the Enzyme Linked Fluorescent Assaysystem kit.

Results: The combined positivity of anti cytomegalovirus IgG and IgM antibodies was 93 (30.40%). About 37 (37.37%) and 28 (34.14%) women were found to be seropositive for cytomegalovirus antibodies who had history of spontaneous miscarriage and recurrent miscarriages respectively.

Conclusion: Higher association of seropositivity for cytomegalovirus IgM and IgG with bad obstetrical history and low economy was found.

Keywords: Adverse pregnancy outcome, Cytomegalovirus, Intrauterine fetal death, Preterm labour.

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INTRODUCTION

Human cytomegalovirus (CMV) is an enveloped DNA virus of herpes family which is predominant universally in all socioeconomics classes¹. Seroprevalence of CMV is varies between 50-85% in developed world and around 100% in poorly developed countries². In a review, Griffith has stated that cytomegalovirus is the most frequent cause of intrauterine infection however it is occasionally blamed as an occupational hazard in working women of reproductive age group³.

CMV is responsible for most of the adverse early pregnancy complications like spontaneous or recurrent miscarriages and certain congenital malformations as well as it has also been isolated in women who had a history of still birth⁴. The birth prevalence of congenital cytomegalovirus infection is estimated at 0.64% and 11% of these infants are symptomatic⁵. CMV is mostly transmitted to the growing fetus during pregnancy as well as when come in direct close contact with young children who have acquired active infection. The rate of transmission of primary infection is high as compared to secondary infection⁶.

In the developed countries the major risk factor

for the congenital infection is reported to be related with maternal primary CMV infection during pregnancy. Several researches have been carried out worldwide based on fetal congenital malformations resulting after CMV exposure^{6,7}. However little literature is available about the women with bad obstetrical outcome and its relationship with CMV seroprevalence. The present study was conducted to find out the prevalence of antibodies against cytomegalovirus and their association with adverse pregnancy outcome in women, at Isra University Hospital Hyderabad.

METHODOLOGY

The present descriptive cross-sectional study was conducted from January to June 2018 at Isra University Hospital (IUH) Hyderabad. A total of 305 women in reproductive age group who had adverse pregnancy outcome visiting to clinic for complaints were enrolled. All the women were counseled and informed verbal consent was obtained for the study. Detailed history was taken regarding socio-demographic profile and adverse pregnancy outcomes were further explored. Adverse pregnancy outcome is defined as unfavorable pregnancy outcome found as consecutive spontaneous miscarriages, intrauterine death, intrauterine growth restriction, stillbirth, early neonatal death and congenital anomalies. However women who had medical, genetic, autoimmune and positivity of other TORCH infections has been excluded from the

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study. The women participating in this study were all healthy women with past bad obstetrical event of not more than of six month duration. The study was approved by the Ethical Committee of Isra University Hospital (IUH). The participants were briefed regarding CMV infections and related possible complications.

A 5ml venous blood sample was taken from each woman and was submitted to the microbiology laboratory of IUH for anti CMV IgG and IgM antibodies analysis. The sera were separated and stored at 40C until analyzed. The anti CMV IgG and IgM antibodies against CMV were detected by using ELISA technique according to the instructions of the manufacture. The cut off values by the manufactures were used to determine the results. Mean ± age, percentages and frequencies were calculated for the data and chi-square test was applied. SPSS-21 was applied for the statistical analysis.

RESULTS

A total 305 women were recruited with adverse pregnancy outcome and their association with CMV antibodies IgG and IgM were assessed. The mean age of study participant in current study was 29 ± 18 years (minimum 17 years, maximum 40 years). Anti CMV IgG/IgM antibodies were found in 93 (30.49%) women, however 212 (69.50%) women were found to be seronegative for CMV antibodies. The positivity for anti CMV IgG antibodies were found in 77 (82.79%) while 16 (17.20%) were found to be positive for anti CMV IgM antibodies.

who are well educated and self employed as shown in table-I.

There is higher association of seropositivity for CMV IgM and IgG with bad obstetrical performance. About 37 (37.37%) women were found to be seroposi-

Table-I: General characteristic of women (n=305) with adverse pregnancy outcome and association with seropositivity for cytomegalovirus (IgM and IgG antibodies).

General Characteristic of study Participants	No. of cases (%)	Seropositivity for IgG and IgM	p-value
Age			
<40 years	162 (53.11)	60 (37.03%)	0.04
>40 years	143 (46.88)	33 (23.07%)	
Parity			
Primipara ¹	108 (35.40)	19 (17.59%)	0.05
Multipara ²	153 (50.16)	31 (20.26%)	
Grand Multi para ³	44 (14.42)	43 (97.72%)	
Educational Level			
Low ⁴	217 (71.14)	59 (27.18%)	0.05
High ⁵	88 (28.85)	34 (38.63%)	
Socioeconomic Status (SES)			
<10,000 PKR	197 (64.59)	69 (35.02%)	0.03
10,000-15000 PKR	61 (20)	15 (24.59%)	
>15000 PKR	47 (15.40)	9 (19.14%)	

tive for CMV IgG antibodies and IgM antibodies who had history of spontaneous miscarriage, whereas 28 (34.14%) for recurrent miscarriages were seropositive for IgG and IgM antibodies shown in table-II.

Legends

1. Primipara: having given birth to only one child

Table-II: Association of seropositivity for cytomegalovirus (IgM and IgG antibodies) with adverse pregnancy outcome in 305 participating women.

Variables of Adverse pregnancy outcome	No. of cases (n=305)	Seropositivity for CMV antibodies		p-value
		Seropositivity for IgG (n=77)	Seropositivity for IgM (n=16)	
Spontaneous Miscarriages ¹	99	29 (29.29%)	8 (8.08%)	0.04
Recurrent Miscarriage ²	82	23 (28.04%)	5 (6.09%)	0.04
Still Born ³	64	16 (25%)	1 (1.56%)	0.06
IUFD ⁴	21	5 (23.80%)	1 (4.76%)	0.06
Preterm labour ⁵	13	1 (7.69%)	-	0.08
IUGR ⁶	17	2 (11.76%)	-	0.07
ENND ⁷	9	1 (11.11%)	1 (11.11%)	0.07

There were significant difference between the CMV IgG/IgM with sociodemographic profile based on age, parity, literacy rate and employment status (p<0.05).The women who were unemployed with poor socioeconomic back ground and have more children showed higher IgG and IgM level compared to those

2. Multipara: having more than one children
3. Grand multi para: condition of having given birth five or more times
4. Low education level: basic primary education only
5. High education level: higher secondary school education or above

Legends

1. Spontaneous miscarriages (abortion): expulsion of products of conception before 20 weeks of gestation when the weight of fetus is 500 gram or less.
2. Recurrent miscarriage: occurrence of three or more consecutive pregnancy loss.
3. Still born: fetal death at or after 20th to 28th weeks gestation without sign of life. IUFD (intra uterine fetal death): fetal/infant death during delivery, which was not associated with improper management.
4. Preterm labour: labour resulting in birth before 37 completed weeks (259 days) of gestational age.
5. IUGR (intra uterine growth restriction): estimated fetal weight is at or below the 10th percentile of gestational age.
6. ENND (early neonatal death): death of a live born with in first seven days of delivery .

DISCUSSION

Human cytomegalovirus (HCMV) belongs to herpes virus family and is associated with persistent, latent and recurrent infection. In developed countries human cytomegalovirus (CMV) infection seroprevalence in pregnant women is reported to be around 42-68% whereas over 95% in developing countries such as China⁸. Besides this, the prevalence of live birth in congenital CMV infection in the developed world is only 0.6-0.7%. Women affected with this virus during pregnancy are prone for miscarriages, stillbirth, birth defects and also puts hazard to attending nursing staff⁹.

It was found in present study that out of 305 study participants, 93 women (30.49%) showed seropositivity for CMV IgG/IgM antibodies. Similarly Sadik *et al* conducted a study in women with bad obstetrical history in south Indian population. He reported presence of IgM and IgG antibodies for CMV in 23.25% of randomly selected 86 pregnant women¹⁰.

In present study most of the seropositive women, showed positivity for IgG antibody against CMV 77 (82.79%) while only 16 (17.20%) were seropositive for IgM antibody. Reason for high prevalence of IgG antibody may be due to random collection of data from non-pregnant women, whereas the infection might be acquired during pregnancy. Similarly Wang *et al* in his study conducted on seroprevalence of cytomegalovirus among women of reproductive age in the United States reported that out of 5714 women included in the

analysis, majority of participants (70%) were IgG +ve¹¹.

Present study revealed that out of 305 study participants, 162 (53.11%) were of less than 40 years of age and out of these i.e., 60 (37%) were seropositive for IgG/IgM against CMV. On the other hand 143 (46.88%) of women were >40 years of age and out of these 33 (23.07%) showed seropositivity for the same antibodies. Similarly Staras *et al* in his study conducted in the United States reported CMV seroprevalence of 58.3% among women of childbearing age i.e., 15-44 years¹². These results signify the prevalence of CMV infection in reproductive age group.

Household income level was found to be inversely associated with CMV seroprevalence in present study. It was found that of 197 (64.59%) participant having low level of income, 69 (35.02%) were CMV seropositive. Whereas 15 (24.59%) from the middle level and 9 (19.14%) from high level of income showed seropositivity for CMV. These results are quite significant as they show that majority of the participants were having low level of income and although the percentage of seropositive women was 35.02 but it make 74.19% of the total 93 seropositive cases which reflect high prevalence of CMV in women of low socioeconomic group. Similar results were reported by Staras *et al* who found 70.8% seropositivity for CMV in the women with low income and 60.5% and 46.6% in women with middle and high income respectively¹².

Comparable results were reported by Enders *et al* who concluded about the association of CMV with socioeconomic status, as CMV seroprevalence in low, middle and upper socioeconomic status was 91.8%, 46.9% and 33.7%, respectively¹³. Supporting the findings Bate *et al* in 2010 reported low socioeconomic status as a strong risk factor for acquiring CMV infection¹⁴.

Present study reveals that of 305 participants, 217 (71.14%) had received primary education while 88 (28.85%) had reached to the senior high school level. Of these, 59 (27.18%) of 217 women with low education level and 34 (38.63%) women with comparatively high education were showing seropositivity. These results reflect the positive relationship between the occurrence of CMV infection and low education level. Regarding the parity, the results revealed that majority of seropositive women i.e., 43 (97.72%) were grand multi para followed by multipara 31 (20.26%). On the other hand only 19 (17.59%) of the total primary para women were seropositive. More or less same results

were reported by Hamdan *et al* who concluded in their study that uneducated women and those having high parity were at increased risk for acquiring infection with CMV. They have reported 46.7%, 41.9%, 10.2% and 1.2% seropositivity in women who were illiterate, received primary, secondary and university level education respectively¹⁵. The above mentioned factors were also reported as risk factors CMV infection in some other studies as well. The authors have concluded that the increased CMV prevalence in these groups may be due to close contact between family members and poor hygiene responsible for transferring contagious secretions^{14,16}.

Present study also evaluated the relationship between prevalence of infection with CMV and spontaneous abortion. These results revealed that out of 305 participating women, 99 (32.45%) had spontaneous abortion of their last pregnancy. Of these 29 (29.29%) women showed seropositivity for IgG against CMV, 8 (8.08%) for IgM. Further, the results also showed that 82 of total study participants were having history of recurrent miscarriage, out of which 23 (28.04%) were showing presence of IgG type of antibodies, while 5 (6.09%) were having IgM antibodies against CMV. These results showed a significant correlation of CMV infection during pregnancy with spontaneous and recurrent abortion. The results are comparable to the results reported by Jasim *et al*, who stated that out of 300 women having bad obstetrical history, 162 women were presented with history of spontaneous abortion and of these, 60.2% women revealed presence of IgM antibodies against CMV in their sera. He further reported that high percentage (12.4%) of repeated abortions was seen in women showing seropositivity for CMV IgM¹⁷. Another study conducted at Al-Diwaniyah on 125 women for evaluation of the seroprevalence of cytomegalovirus and toxoplasmosis had reported highest prevalence of CMV infection in the first trimester in women with history of multiple abortions for both pathogens¹⁸.

The results of the present study also showed that in women who presented with history of stillbirth of one or more of her children, 16 (25%) and 1 (1.56%) women showed seropositivity for IgG and IgM antibodies respectively at the time of evaluation in non-pregnant state. More or less same results have been documented by Howard *et al* who has reported that intrauterine deaths including stillbirths may be caused by CMV infection as 10 (9%) stillborn infants were CMV positive out of total of 107 infants in his study¹⁹.

Likewise, another study conducted by Iwasenko *et al* regarding CMV and its role in stillbirths, done on placenta and fetal tissue from a series of 130 stillborn infants has reported presence of DNA of CMV in 15% of specimens. This is again in favour of the results of present study and show strong association and a possible etiological role of CMV with bad pregnancy outcome²⁰. Same type of study was conducted by Padmavathy *et al* in 2013 on the association of TORCH infections with bad pregnancy outcome. The author reported the CMV IgM and IgG positivity as 9.2% and 95.4% respectively²¹.

The results of present study also indicate that 21 of study participants (out of 305) were having history of intra uterine death of their last baby. Out of these, 5 (23.80%) women were showing seropositivity for IgG antibody, while only one woman was having IgM antibodies. Comparatively lesser number 8.4% cases with history of intrauterine fetal deaths were reported by Padmavathy²¹.

The results also signify that 17 of total study participants were presented with history of IUGR of their last baby. Out of these 2 (11.76%) were found to have IgG antibody. These results are also quite significant as they show that some of the cases of IUGR were due to infection by CMV. Hendrix has put into same words in a seminar in Perinatology as fetal infections are responsible for up to 10% of growth restriction cases and presently the most common causes are toxoplasmosis and cytomegalovirus in developed countries²². Similarly Bamberg C has narrated about the causes of IUGR in a seminar in fetal and neonatal medicine as "congenital infection by CMV during early gestational time is important beside familial lesions leading to genetic anomalies"²³.

In addition to other bad pregnancy outcomes, CMV also has effects of preterm labour. In present study, it was found that out of 305 study women, 13 were presented with history of preterm labour in their last pregnancy. It was noted that out of these 7.69% were showing presence of IgG type of antibodies against CMV. Romero *et al* has focused on effects of inflammatory reactions on fetal injury and pre term parturition in a seminar on Fetal and Neonatal Medicine. He has stated that inflammation/Infection is a frequent and important mechanism of disease in PTL and delivery and CMV is one of the most important causes²⁴.

The results of present study also reflect the important association of CMV infection during preg-

nancy and its effects on fetus in early neonatal period. It shows that out of 305 study participants, 9 women presented with history of early neonatal death of their last baby and out of these; 11.11% were showing presence of IgG antibody while same percentage were showing presence of IgM type of antibody against CMV. Boppana has reported a study on 106 neonate with symptomatic congenital CMV infection and has concluded that neonate with symptomatic congenital CMV infection suffer from multisystem diseases with significant morbidity and mortality as 12% of infants died during the first week of life²⁵.

CONCLUSION

It can be concluded from the results of the present study that bad pregnancy outcome is common in region of Hyderabad and its peripheral areas and CMV is one of the important causes. The women in this area are not aware of this, hence it seems to be more common in women with low education level and low socioeconomic status. Moreover, CMV infection during pregnancy is responsible for a considerable number of cases of spontaneous and recurrent miscarriages, still birth, IUFD, preterm labour, IUGR and ENND.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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