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Latent and reactivation Cytomegalovirus (CMV) infection can cause severe fetal sequelae despite pre-conceptional immunity

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ABSTRACT— Evidences had documented a causal relationship between human cytomegalovirus (CMV) infection and Bad Obstetrical History (BOH). However, a recurrent or latent CMV infection or altered immune response to CMV is resulted in recurrent pregnancy loss (RPL) is unsolved. We investigated CMV infection and antibodies to CMV after urea treatment in women with Bad Obstetric History (BOH). This case-control study was conducted on 143 women with BOH recruited to gynecology and obstetrics department clinic in Benghazi (Libya). Patients were evaluated for anti CMV IgG and IgM antibodies and IgG urea treatment using the enzyme linked immunosorbent assay method. Student's t-test and Chi-square test were used to analyze the data. Two cases (1.4%) of positive anti-CMV IgM was detected in each group. Anti-CMV IgG positivity was more frequent in patients (39.9%. there was Big significant differences between the habitual abortion (HA) group compared to the other BOH manifestations. IgG concentration was significantly higher in HA seropositive cases than seropositive BOH patients. We found that previous exposure to CMV was significantly higher in patients with Habitual abortion than the other BOH group. Moreover, association was found between IgG urea treatment and HA. Further investigations are under way to find whether latent CMV infection starts an indirect process of autoimmune etiology in RPL or women with RPL have recurrent or reactivation of CMV infection.

KEYWORDS: Urea treatment, cytomegalovirus, infection, recurrent pregnancy loss, Habitual Abortion, Bad Obstetric History, IgG, IgM

1. INTRODUCTION

Congenital CMV infection is a major intrauterine transmitted viral infection responsible of the most frequent congenital infection worldwide with an incidence of 0.2–2.2% of live births. Rate of transmission to the fetus ranges between 15% and 75% and the primary infections in the first half of pregnancy period appear to have the worst outcomes [1].

Maternal infections with this virus have been proposed as a significant factor in causing poor Bad Obstetrical History (BOH). Whether primary infection or reactivation of CMV in a pregnant woman is the main cause of pregnancy loss is still under unsolved. Results have been controversial, and with the underlying mechanisms still unclear [2- 9]. Number of studies detected high presence of CMV antigens in tissues from aborted fetuses [10], others documented a higher CMV seropositivities [11].

Studies showing a high risk of habitual abortion with CMV infection exist [12], as well as indications that did not reached a conclusive conclusion appeared too [13].

Habitual abortion is referred to as two or more consecutive abortions earlier to 22nd gestational weeks. Cumulative data indicating that around 15% of pregnant women experience sporadic pregnancy loss, with only 0.4-1% of them experience two and three consecutive abortions. Etiology of HA is diverse and few evidence-based diagnostic and treatment approaches are available. Etiologic factors associated with HA consist of anatomical, immunological, genetic, endocrine, infectious, coagulative, as well as environmental factors [14], [15]. One research team showed high prevalence and high antibody titers to CMV in HA cases [16]. On the other look. Investigations presented comparable and even less prevalence of antibodies to CMV among women with HA than normal pregnant women [17], [18]. Contrary to that information, reports on HA might have some selective immunological unresponsiveness to CMV. Autoimmune manifestations and raised gammaglobulin in RPL cases may have resulted in false positivity in CMV antibody concentrations [19].

Many previously appeared studies on the association between CMV infection and the various BOH were mostly based on incomplete, simple, questionable serological tests. Also, sample sizes were small among many of these studies. Considering the lack of data on the etiology of BOH, and also regarding the suggested role of altered immune responses, we attempted in evaluating and comparing humoral immunological responses to CMV in women with HA and other bad obstetrical history (BOH) using IgG and IgM CMV antibody by the quantitative urea denatured IgG ELISA assay to find the type of BOH most frequently associated with CMV seropositivity. We also take the advantages of urea modified ELISA for the distinction between primary and reactivation CMV infection and their roles in the various BOH manifestation in our group of patients.

2. Material and methods

This is a hospital based seroepidemiological study conducted in the Department of Obstetric and Gynecology in Jomhoriya hospital –Benghazi, Libya on 143 pregnant women with bad obstetrical history (BOH). Women were recruited only if they developed two or more HA, intrauterine fetal or neonatal deaths (IUFD, IUND) stillbirth (SB) or low birth weight infants (LBW)or off springs with multiple congenital anomalies (MCA). All women were given informed consent and interviewed to ascertain of their demographic, medical and obstetric information's. Data were recorded in a specially constructed questionnaire after taking consent and full history. women were thoroughly examined by trained gynecologists for the probable factor(s) responsible for their past reproductive losses.

Blood samples were obtained and serum was separated and stored at -20◦C until processing. The following kits were made available:

A. CMV IgG ELISA from BIOKIT, S.A. SPAIN.

B. CMV IgM ELISA from BioCheck, Inc. USA.

Both qualitative and quantitative testing of maternal serum for CMV IgG and IgM antibodies were done according to the instruction provided by the manufacturer.

A step of urea denaturation was included to distinguish the primary from secondary (reactivation) CMV infection. Urea is included in the wash step of the standard IgG ELISA testing. This resulted in the removal of low-avidity antibodies, which are the antibodies produced early in infection [20].

Pregnant women with low titer were considered having primary maternal whereas those with high responses were taken as having reactivation maternal infection [21]. Accordingly, we were able to group recruited patients into the following groups:

1- CMV seronegative: when both CMV-IgM and -IgG were negative.

2- IgG- CMV seropositive: when CMV-IgM negative but CMV-IgG was positive.
3- Primary CMV infection: when CMV-IgM positive and low IgG positivity (>0.25-1 IU/ml)
4- Recurrent CMV infection: when women are CMV-IgG positive antibody with high concentrations (>5-20 IU/ml)
5- Undefined CMV infection: when women were with moderate IgG concentration (>1-5 IU/ml)

Data obtained in this study were analyzed using SPSS software (Version 16.0, Licensed to TEAM EQX). To determine possible association, every variable was compared to CMV IgG and IgM seroprevalences in 2 x 2 table using chi- square (x^2) test and Fisher's exact test. Effects were considered significant if P-value of less than 0.05 ($p<0.05$) is obtained.

3. Results

In our study, out of the 143 cases with bad obstetric history BOH), the total number of CMV IgG positive cases were 57 (39.9 %). We selected to study their age range, residency, occupation and history of blood transfusion as demographic features and all showed statistically significant effects on the IgG seropositivity (Table -1). IgG seropositivity in relation to the type of BOH is depicted in Table-2. Forty-five (45) out of the overall 117 HA cases (38.5%) (78.9% of the 45 positive cases out of the overall 57 positive women) were positive. The rest of BOH manifestations resulted in the following observations: Six (50 %) out of 12 patients with intrauterine fetal death (IUFD) were IgG positive. In the group of women suffered of intrauterine neonatal death (IUND), 8 (30.8%) out of 26 cases were positive. Those with Multiple Congenital Anomalies (MCA), their total number were 23 with 10 (43.5%) were IgG positive. Of the total positive women MCA represent 17.5%. In the low birth weight group (LBW), 10 out of 24 total cases were positive (41.7 %), whereas in the 6 still birth group (SB) 2 (33.3 %) only were positive. Differences between these data were statistically significant (table-2). Analysis of the total number and percentages of IgG positive cases in the habitual abortion women which were 45 out of the 57 (78.9 %). comparison of these data with the information reported in the rest of BOH cases which were 36 out of the 57 (63.1%). Differences between these figures and the results obtained in the habitual abortion group were highly statistically significant (Table 2). The total number of women suffered of BOH except HA were 91 with 36 cases IgG positive (63.1 %). These differences were statistically significant when compared to those with HA.

In the present study, we recorded only 2 women (1.4%) were CMV IgM antibody positive. Both of them belonged to habitual abortion group. One was IgG positive while the second was IgG negative. Their age ranges was 18- 27 years (not shown in a table).

Results depicted in Table-3, represent the IgG seropositivity plotted quantitively after urea treatment. Low positive CMV IgG concentrations (0.25-1 IU/ml) were demonstrated in five (3.5%) women only. Moderate concentrations (1-5 IU/ml) were shown in 20 (13.9. %) of the positive cases. The rest 32 (22.4%) positive women were presented with strong IgG concentration (>5-20 IU/ml). Statistical significance indicated that differences between these data were significant.

In Table-4, 29 (90.6%) of the strong responders belonged to the habitual abortion women compared to only 2 out of 5 only (40%) which were weak responses in this group. The other BOH manifestations were far below the data obtained in the HA cases. These differences were highly significant.

Table 1: CMV IgG antibodies and risk factors in the BOH group

Demographic parameter	No. tested	IgG-Positive No.	IgG positive %	Probability
Total number of patients	143	57	39.9%	
Age/ years				P ≥ 0.05
18-27	12	5	41.7%	
28-35	66	25	37.9%	
36-44	65	27	41.5%	
Residency				P= 0.0068 (p≤0.05
Urban	100	43	43%	
Rural	43	14	32.6%	
Occupation				P=0.0184
Employee	55	19	34.5%	
Nonemployee	88	38	43.3%	
Blood transfusion				P ≥ 0.05
Received	23	8	34.8%	
Never	120	49	40.8%	

Table 2 CMV IgG antibodies and bad obstetric history.

Bad obstetric history	No. tested	IgG-Positive		%out of total +ve (57)	Statistical significance
		No.	%		
Habitual Abortion (2 & more)	117	45	38.5%	78.9%*	P=0.036 (p≤0.05) Highly significant
Intrauterine fetal death (IUFD)	12	6	50%	10.5%	P=0.0265 (p≤0.05) Highly significant
Intrauterine neonatal death (IUND)	26	8	30.8%	14.0%	P= 0.032 (p≤0.05) Highly significant
Multiple Congenital Anomalies (MCA)	23	10	43.5	17.5%	P=0.018 (p≤0.05) Highly

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					significant
Low birth weight (LBW)	24	10	41.7	17.5%	P=0.032 ($p \leq 0.05$) Highly significant
Sill birth (SB)	6	2	33.3	3.5%	
IUFD+IUND+MCA+ LBW+SB	91	36	39.5%	63.1%*	($p \leq 0.05$)*

Table 3 CMV IgG antibodies expressed quantitatively (IU/ml).

CMV IgG conc. IU/ml	No.	%	Probability
Negative <0.25	86	60.2	
Positive (low concentration) >0.25-1	5	3.5	($p \leq 0.05$)
Positive (moderate concentration)>1-5	20	13.9	($p \leq 0.05$)
Positive (high concentration) >5-20	32	22.4	($p \leq 0.05$)

Table 4 Strong and weak positive CMV IgG levels and BOH.

CMV IgG conc. IU/ml	No. of cases with the different BOH manifestations							
	Total No. (%)	HA	IUFD	IUND	C.A	LBW	SB	P values
>5-20 High responder	32/57(22.4%)	29/32 (90.6%)	7(21.8%)	8 (25%)	4(12.5%)	11(34.4)	1(3.13%)	0.0287 ($p \leq 0.05$) Highly significant
0.25-1 Weak responder	5/57 (3.5%)	2 /5 (40%)	1(20%)	0	0	2 (40%)	0	0.0467 ($p \leq 0.05$) Highly significant

4. Discussion

The key aim of the present study was to evaluate if exposure/infection to CMV and/or a disordered immunological response to CMV has an effect on the various BOH manifestations in women in our population. For this aim, we assessed the anti-CMV IgG and IgM specific antibodies along with IgG concentration after a step urea denaturation. This algorithm seems a solid and reliable proof to differentiate a recurrent /reactivated infection from primary infection [20], [21].

The present data as well as many previous ones provided information on that the pre- pregnancy immunity against CMV is only resulted in incomplete protection against CMV infection. Furthermore, undesirable outcomes can occur in infected children born to women who were seropositive prior to pregnancy [22], [23]. In-utero transmission of CMV in women with preexisting humoral immunity can occur secondary to

virus reactivation [24] or infection with a different human CMV strain (reinfection) during conceptus [25]. Immunization schedules against CMV infection seems only partially protective to either reinfection or vertical transmission of infection from mother to fetus [26]. [27], however indicated promising remarks via using passive immunization against congenital CMV infection.

The present study mostly agreed with the conclusions given in [28] in that approximately one third of those with humoral immunity had CMV reinfection during the follow-up visit. Further, more data proved that the chance of congenital CMV infection increases with increasing maternal CMV seroprevalence [29]. It seems that with the high CMV seroprevalence, the number of pregnancies at risk for reactivation is also increased, probably, due to a higher prevalence of risky behaviors in the population. In a population with high seroprevalence, a pregnant woman has a more likelihood of exposure to CMV-infected people. Hence, in those with high risk practice, seropositive women have a higher chance of reactivation, while, seronegative women have a higher possibility of primary infection [30]. Preventive measures therefore, should be allocated to decrease the perinatal mortality and morbidity related to CMV infection and to ensure that women will not become infected with CMV during their gestation. Thus, pregnant women should be encouraged to implement more preventive measures.

In the women of the current experiment, we noticed that habitual abortion patients were significantly more seropositive than those with other BOH suggesting that exposure to CMV might be a risk factor for habitual abortion. This might occur through the mechanism of the recurrent reactivation of CMV infection during the consequent conceptus. The patients had also higher IgG titer either because of hyper-responsiveness or due to re-exposure to CMV agent. Both the two possibilities exist indicating altered immune responses during HA manifestations. Either the recurrent exposure to CMV could lead to HA, or patients with HA have altered immune response to CMV leading to higher IgG concentration.

In agreement with our results, [14] found more frequent seropositivity and higher levels of antibodies in women with RPL than controls. This data probably suggested that abortion might have resulted from fetal infection due to reactivation of chronic CMV infection in the course of pregnancy.

Contrary to the present study, only scanty reports are available on the causal relationship between CMV infection and HA with controversial results. [16- 18] e.g. On a large sample of recurrent pregnancy loss (RPL) cases and controls found identical seropositivity prevalence (78% vs. 81.1%) [16]. In their study, [18] on women with RPL of unknown etiology found only 35% seropositive cases compared to 65% in controls. Further investigators also found lower seropositivity in RPL women compared with age-matched female controls [19].

Our research and many other similar studies might indicate that women with RPL have difficulty in responding to CMV as well as the other BOH manifestations. The present results showed the significant association of HA and recurrent CMV infection when compared with the various other BOH problems. Our selection of comparing HA with the many other BOH manifestations seems superior than taking normal pregnant women as control. A number of previous studies used polymerase chain reaction method as indicator of congenital CMV infection but without finding CMV in gestational tissue of women with RPL [31], [32] suggesting that CMV infection in the gestational tissue is not the direct cause of abortions in RPL cases and might bring attention on the role of immune responses in the RPL causation. Differences between the present study results and the published ones can also be due to differences in the studied population. Further, it is well-known that epidemiology of CMV infection is different among different populations.

Of the remark of the present study the observation that CMV seropositivity increase with increasing age of the women (more than 131 cases were 28-year-old and more). Similar conclusion was given by [16] who found that seropositivity of CMV in RPL cases raised with increasing age (from 76.5% in younger than 20 years to 91.4% in older than 34-year-old women). Future larger multi-socioeconomic characteristics features, as well as different components of the immune response to CMV need to be elucidated to get more clear-cut conclusion.

Despite what is mentioned concerning age and CMV infection, reports on that elderlies appear to be resistant to CMV infection because of the development of CD28 effector cytotoxic T lymphocytes in those patients [35]. Others insisted that this is a characteristic feature of all age groups but is most deep in elderlies (41). Debates regarding maternal age and CMV infection is noticed as many investigators agreed with us in that elderly women were at a higher risk of CMV infection [38], [36]. Other have reported the reverse [42] or absence of variation due to age [33]. The above findings, however, are consistent with the finding that CMV IgM can be produced over the course of a lifetime after primary infection or also as a result of reinfection or reactivation [43], [44]. This indicate that some older cohorts may be likely to have recurrent episodes of CMV infection as well as the younger people do have a primary infection [33].

The present study also shows an overall seroprevalence of CMV IgG (39.1%) in Libyan BOH patients at the city of Benghazi, with significant differences between the rate in women with HA compared to the levels in the other BOH manifestation. To our knowledge, in Libya, no previous data on the role of CMV in BOH women were available. The current CMV infection rates of our study population is identical to that reported in many Arab countries e.g. in the Jordanian BOH women [40].

Another way to elucidate for correlation between BOH and CMV infections was the linking of the quantitative IgG concentrations with the type of the BOH manifestations (table 3, 4): 90.6% of those with high IgG concentrations were suffering of habitual abortion in comparison to only 40% of the low IgG responders. The present study agreed with many earlier ones in that, the natural course of active CMV infections are usually associated with raised IgG titers [31], [32].

CMV IgM was positive in two women only (1.4%); one was IgG positive whereas the other was IgG negative. This is probably an indication that both cases suffered of an early acute infection. [34] agreed with us in detecting extremely low rate of 0.54% in Iranian pregnant women. Whereas, other investigators reported high levels of IgM seropositivities [33]. In our opinion, the differences in IgM seroprevalences are related to the overall prevalence of CMV infection in the population.

In conclusion, it seems that active CMV infection in Libyan pregnant women are relatively low (1.4%). We failed of finding an identifiable risk factors for CMV IgM because of the relatively small number of positive cases, and also due to the fact that most of the recruited cases were with high IgG reactivity and high avidity and therefore presumably came from a non-primary CMV infection, thus less associated with identifiable risk factor than a primary infection as shown by [35]. In addition, the two IgM positive sera might be false positive, which is known to occur with CMV IgM testing [36].

There was significant differences in IgG seroprevalence among the three selected age groups as well as those received blood transfusion. These findings are consistent with that reported in many other places [37]. Concerning, residency and occupation both resulted in statistically significant differences too. There was a higher significant prevalence of CMV IgG among working women compared to housewives. By contrast, a previous study indicated that CMV IgG seropositivity occurred more often in housewives compared to

women with other occupations [38]. We believe that the Illiteracy and low education levels should be forwarded as risk factors for the increased susceptibility to CMV infection. The explanation is perhaps because of the direct contact with contagious secretions from their own children as well as poor hygiene practiced by these women during their daily life [39- 42]. Furthermore, low socioeconomic status is a strong risk factor for CMV infection as shown by [40]. However, in Libya and the various Arab countries, it is difficult to investigate the socio-economic status of the pregnant women due to culture- based attitude of generous hospitality toward guests and family members which make measuring such parameters difficult.

Maternal CMV infection in Libyan population still represent a health problem that should be considered by local healthcare providers.

Routine nationwide screenings for CMV should be thoroughly examined, although high cost effectiveness issues must be considered before the implementation of such screening's programs.

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