



Original Research

The Association of Antiphospholipid Syndrome Stimulated by Cytomegalovirus Infection with Pregnancy Outcome Among Women with Bad Obstetric History in Babil/ Iraq

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Abstract:

Earlier studies have shown a significant correlation between Cytomegalovirus (CMV) infectivity and adverse pregnancy outcome, worldwide. A correlation also has been shown for Antiphospholipid (APL) syndrome and pregnancy outcome in developing countries like Iraq. However, there is a paucity of data informing the association of both APL and CMV infections in pregnancy outcome from that part of the globe.

This descriptive case control study was undertaken in Babil/ Iraq to determine the local seroprevalence of APL in women of child bearing age with and without CMV infection, to identify the socio-demographic factors associated with them, and to investigate whether or not it is important to screen post CMV women with Bad Obstetric History (BOH) for APL antibodies. This study found an overall seropositivity of 25.7% for APL IgG among patient group. The seroprevalence of past and current infections of APL levels was highest amongst those who were educated for < 6 years (25.8, 75)% and overcrowded (22.9, 75)%, respectively. A significant correlation ($P=0.04$) was found between APL IgG and abortion. A significant correlation ($P= 0.02$) was also noted for concurrent infection with both CMV+ve & APL+ve and abortion. The seroprevalence of APL IgG among age group was highest (31%) among patient aged 21-29 Yrs old, whereas for APL IgM, the peak (50%) was at age >30-39. This study concludes that APL screening of women post CMV infection might be of high importance especially for women with BOH. This will effectively aid to implement the adequate intervention methods that improve pregnancy outcomes.

Key words: Antiphospholipid, APL, CMV, Cytomegalovirus, pregnant, ELIZA, Iraq.

Introduction:

APS is an autoimmune thrombophilic disease associated with vascular thrombosis (artery/vein) and fetal loss during pregnancy, marked by the presence of several types of antiphospholipid antibodies including, anti- beta2 glycoprotein 1 antibodies (β 2GP1), lupus anticoagulant (LA) and Anticardiolipin antibodies (ACA) ⁽¹⁾. These antibodies are directed and attack phospholipid binding proteins rather than phospholipid itself ^(2,3). APS is termed primary APS, when APL antibodies exist in blood of healthy individuals, and Secondary APS, when these antibodies are combined with autoimmune disease, mainly Systemic Lupus Erythematosus ⁽²⁾. Currently, the standard diagnosis of APS requires at least one clinical and one laboratory indicator. Clinical measurement comprises the presence of at least one fetal loss of a morphologically normal fetus at $\geq 10^{\text{th}}$ week of gestation. Laboratory measurement involve the detection of one of the APL antibodies in patient's blood twice at 12 weeks apart ⁽⁴⁾. Previous studies investigated the pathological role of antiphospholipid syndrome in pregnancy loss, mainly during third trimester ^(5, 6, 7). Other studies have investigated the role of Anticardiolipin antibodies (ACL) ⁽⁴⁾, Anti-beta2 glycoprotein 1 antibody (β 2GP1) ⁽⁸⁾ and APL Antibodies with fetal loss ⁽⁹⁾.

Active Human Cytomegalovirus HCMV infections causes permanent disabilities for about 0.1-0.2% of all pregnancies worldwide. These disabilities caused by HCMV may be lifelong and / or severe including blindness, intellectual disability, microcephaly, deafness, cerebral palsy, developmental delay, and death in rare cases ⁽¹⁰⁾. About 0.5 – 1.1% of all pregnancies worldwide happen in women with active HCMV infection. The outcome for 90% of these pregnancies can be asymptomatic infants. Nevertheless, about 5-10% of these asymptomatic infants ultimately die of HCMV related complications ⁽¹¹⁾.

Several studies indicated APS is induced post microbial infections including; viral (Cytomegalovirus, Adenovirus), bacterial; (*Mycobacterium tuberculosis*) and parasitic

infections including *Plasmodium spp* ⁽²⁾. A recent study from De Carolis (2018) ⁽¹²⁾ found a significant association between false positive TORCH (Toxoplasma, Rubella, CMV and Herpes) results with APL antibodies among healthy pregnant women.

Epidemiology

The prevalence rate of APL antibodies in healthy individuals range from 1-5% ⁽¹³⁾. A study from Love and Santoro (1990) ⁽¹⁴⁾ analysed 29 published series with a sample size over 1000 patients. This study confirmed the prevalence of APL antibodies in patients with and without Systemic Lupus Erythematus (SLE) and found a frequency of 34% for the LA and 44% for ACL amongst SLE patients. In addition, the study suggested an association between APL antibodies and fetal loss in SLE women. APL antibodies are usually involved with slowly developed thrombosis and adverse pregnancy outcome including frequent spontaneous abortion, preeclampsia, intrauterine growth restriction and late fetal loss. The incidence of fetal loss among primary APS seropositive healthy women ranges from 34% to 76% ⁽¹⁵⁾.

Globally, there is a difference in the CMV prevalence in women with BOH, fluctuating from 14.2% in Iran to 91.05% in India ⁽¹⁶⁾. Interestingly, amongst Arab women, seroprevalence diverges from 77.8% in Iraq to 88% in Jordan for pregnant women ⁽¹⁷⁾ and from 4.8% in Iraq to 95% Jordan ⁽¹⁸⁾ for those with BOH.

Study aims and objectives

Although there is accumulation of literature informing the seroprevalence of APL and CMV worldwide. There is however rare data informing the association between APL and CMV in fetal loss at local levels in Babil/ Iraq especially among women of child bearing age.

This descriptive case—control study is performed to determine:

1. The relation between CMV and APL in pregnancy outcome among women of child bearing age in Babil/ Iraq,

2. The impact of socio-demographic variables on CMV and APL infection rate among women of childbearing age who have had bad obstetric history (BOH).
3. To investigate whether or not it is important to screen post CMV women of child bearing age for APL antibodies.

Materials & Methods:

Blood samples were collected from February 2022 until December 2022 from 60 women of child-bearing age (15-45 years old) with and without CMV infection. To ensure a good spread of the subjects, women mainly with a CMV IgG and/or IgM positives, were identified and recruited from the private labs and the Primary Healthcare Centers situated in urban and rural areas in Al Hamza district in Babylon

Governorates. 15 women who did not meet the study criteria and had missing data were excluded. Of the remaining, 45 members of the study population, 35 (77%) were CMV positive IgG and/or IgM and were considered as patient group, while 10 (23%) were CMV negative and considered as negative control. Sera were consequently diagnosed for APL IgM and IgG antibodies using Antiphospholipis ELISA kits which was commercially available from Calbiotech, USA. ELISA test was performed according to the manufacturer's instructions.

Results:

The seroprevalence of APL IgG among patient group was 25.7% (9 of the 35) tested positive, while for the control group was only 10% (1 out of 10) tested positive for the APL IgG. There is however no significant correlation (Table 1).

Table 1: Seroprevalence of APL IgG between study group.

Seroprevalence of APL IgG			control	patient	Total
APL IgG	negative	Count	9	26	35
		% within patient and control	90.0%	74.3%	77.8%
	positive	Count	1	9	10
		% within patient and control	10.0%	25.7%	22.2%
Total		Count	10	35	45
		% within patient and control	100.0%	100.0%	100.0%
Pearson Chi-Square			1.1		
P value			NS		

The seroprevalence of APL IgM among patient group was 11.4% (4 of the 35) tested positive, while for the control group was only 0% (none of

10) tested positive for the APL IgG. There is however no significant correlation (Table 2).

Table 2: Seroprevalence of APL IgM between study group.

Seroprevalence of APL IgM			control	patient	Total
APL IgM	negative	Count	10	31	41
		% within patient and control	100.0%	88.6%	91.1%
	positive	Count	0	4	4
		% within patient and control	0.0%	11.4%	8.9%
Total		Count	10	35	45
		% within patient and control	100.0%	100.0%	100.0%
Pearson Chi-Square			1.2		
P value			NS		

Interestingly, 77.1% of the patient group (CMV IgG+ve) were aborted women, compared to 10% of the control group (CMV IgG-ve) were aborted. The association between CMV IgG and the abortion was found to be significant at P value of <0.01 . The χ^2 abortion status * CMV IgG was 14.94 at a 95% confidence interval (CI).

Of those tested APL IgG+ve, 90% found to be aborted women, compared to 54% abortion cases

amongst those tested APL IgG-ve. The association between APL IgG and the abortion was found to be significant at P value of 0.04. The χ^2 abortion status * APL IgG was 4.22 at a 95% confidence interval (CI). Of those tested APL IgM+ve, 100% found to be aborted women, compared to 58% abortion cases amongst those tested APL IgG-ve. These results however were non-significant (Table 3).

Table 3: Prevalence of CMV IgG, APL IgG and IgM in relation to abortion status.

			CMV IgG			APL IgG			APL IgM		
			Control group	patient group	Total	IgG -ve	IgG +ve	Total	IgG -ve	IgG +ve	Total
Abortion status	non aborted	Count	9	8	17	16	1	17	17	0	17
		%	90.0%	22.9%	37.8%	45.7%	10.0%	37.8%	41.5%	0.0%	37.8%
	aborted	Count	1	27	28	19	9	28	24	4	28
		%	10.0%	77.1%	62.2%	54.3%	90.0%	62.2%	58.5%	100%	62.2%
Total		Count	10	35	45	35	10	45	41	4	45
		%	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Pearson Chi-Square			14.91			4.22			2.6		
P Value			<0.01			0.04			NS		

CMV IgG levels were highest among educated for <6 years (85.7%), those living in overcrowded situations (91.4%). Evidence of past infection of APL, i.e. positive IgG levels was highest amongst those who were educated for < 6 years (25.8%)

and overcrowded (22.9%). Evidence of current infection of APL, i.e. positive IgM levels was highest amongst those who were educated for < 6 years (75%) and overcrowded (75%) (Table 4).

Table 4: Prevalence of CMV IgG, APL IgG and IgM in relation to education and crowding index												
			CMV IgG		Total	APL IgG		Total				APL IgM
			CMV-ve	CMV+ve		IgG-ve	IgG+ve		IgM-ve	IgM+ve		
EDU LEVEL	Educated for <6 yrs	Count	1	30	31	23	8	31	27	3	31	
		%	10.0%	85.7%	68.9%	74.2%	25.8%	100.0%	65.9%	75.0%	68.9%	
	educated for >6 years	Count	9	5	14	12	2	14	14	1	15	
		%	90.0%	14.3%	31.1%	85.7%	14.3%	100.0%	34.1%	25%	31.3%	
Total		Count	10	35	45	35	10	45	41	4	45	
		%	100.0%	100.0%	100.0%	77.8%	22.2%	100%	100.0%	100.0%	100.0%	
Pearson Chi-Square			20.29			2.4			1.9			
P value			<0.01			NS			NS			
Crowding	not crowded	Count	7	3	10	8	2	10	10	1	11	
		%	70.0%	8.6%	22.2%	80.0%	20.0%	100.0%	24.4%	25%	49.9%	
crowded		Count	3	32	35	27	8	35	31	3	35	
			%	30.0%	91.4%	77.8%	77.1%	22.9%	100.0%	75.6%	75.0%	77.8%
Total			Count	10	35	45	35	10	45	41	4	45
			%	100.0%	100.0%	100.0%	77.8%	22.2%	100.0%	100.0%	100.0%	100.0%
Pearson Chi-Square			16.98			0.034			1.2			
P value			<0.01			NS			NS			

Of the 33 single infection studied (positive only for CMV IgG), 51.5% were not aborted, and 48.5% were aborted. However, of the 12 concurrent infection cases studies (positive for both CMV IgG and APL IgG and/or IgM), 100% of these patients were found to be aborted. The association between infection status and the abortion was found to be significant at P value of 0.02. The χ^2 abortion status * the infection type

whether single or concurrent was 9.93. The chi squared values and p-values indicate that χ^2 figures for women reported with abortion both for CMV IgG and APL IgG was significant at a 95% confidence interval (CI). The χ^2 Abortion status * CMV_IgG was 14.91 at p value of <0.01, while the χ^2 of Abortion status * APL_IgG was 4.22 at a p value of .004 (Table 5).

Table 5: Abortion status * concurrent infection Crosstabulation

Table 5: Abortion status * concurrent infection Crosstabulation					
			Infection		Total
			Single	Concurrent	
Abortion status	non-aborted	Count	17	0	17
		%	51.5%	0.0%	37.8%
	aborted	Count	16	12	28
		%	48.5%	100.0%	62.2%
Total		Count	33	12	45
		%	100.0%	100.0%	100.0%
Pearson Chi-Square			9.93		
P Value			0.02		

For the patient group, CMV IgG was positive for 3 of the 35 (8.6%) of the ≤ 20 yrs age group, 13 of the 35 (37%) of the 21-29 yr age group, 14 of the 35 (40%) of the 30-39 yrs age group, and 5 of the 35 (14.3%) of the ≥ 40 yrs age group.

Regarding APL IgG, 1 of the 6 (16.7%) of the ≤ 20 yrs age group were positive for IgG, 5 of the 16 (31%) of the 21-29 yr age group were positive for IgG, and 3 of the 15 (20%) of the 30-39 yrs age group were positive for IgG, and 1 of the 35

(12.5%) of the ≥ 40 yrs age group were positive for IgG. For APL IgM, 1 of the 6 (25.0%) of the ≤ 20 yrs age group were positive for IgG, 1 of the 16 (25%) of the 21-29 yr age group were positive for IgG, and 2 of the 15 (50%) of the 30-39 yrs age group were positive for IgG, and 0 of the 8 of the ≥ 40 yrs age group were positive for IgG (Table 6). There is however no significance correlation between age group with APL infections.

Table 6: Prevalence of CMV IgG, APL IgG and IgM in relation to age groups

			CMV IgG		Total	APL IgG		Total	APL IgM			
						IgG-ve	IgG+ve		Total	IgG-ve	IgG+ve	Total
			Control group	Patient group								
Age group (Binned)	<=20	Count	3	3	6	5	1	6	5	1	6	
		%	30.0%	8.6%	13.3%	83.3%	16.7%	100.0%	12.2%	25.0%	13.3%	
	21~29	Count	3	13	16	11	5	16	15	1	16	
		%	30.0%	37.1%	35.6%	68.8%	31.3%	100.0%	36.6%	25.0%	35.6%	
	30~39	Count	1	14	15	12	3	15	13	2	15	
		%	10.0%	40.0%	33.3%	80.0%	20.0%	100.0%	31.7%	50.0%	33.3%	
	>=40	Count	3	5	8	7	1	8	8	0	8	
		%	30.0%	14.3%	17.8%	87.5%	12.5%	100.0%	19.5%	0.0%	17.8%	
Total		Count	10	35	45	35	10	45	41	4	45	
		%	100.0%	100.0%	100.0%	77.8%	22.2%	100.0%	100.0%	100.0%	100.0%	
Pearson Chi-Square			5.971			0.71			0.6			
P value			NS			NS			NS			

Discussion:

Earlier studies have shown significant correlation between CMV infectivity and adverse pregnancy outcome. A correlation also has been shown for Antiphospholipid syndrome APS and pregnancy outcome ^(5,6,7). However, there are paucity of literature investigating the association of both APL and CMV infections and their possible influences on pregnancy outcome.

Several philosophies have emerged and explained the pathophysiology of thrombosis among acute CMV and/or APS patients. For APS patients, one of the theories is that; APL antibodies usually trigger an overproduction of tissue factor and thromboxane A2 via activating the production of platelets, endothelial cells and monocytes. The association of these factors with the expected changes in the hemostatic system for pregnant

women will in turn result in hypercoagulation which is the main reason for thrombosis that trigger many of the pregnancy complications associated with APS ⁽¹⁹⁾.

For CMV positive patients, one of the theories suggests that post endothelial cells infection by CMV, the adhesion molecules and tissue factors will be expressed excessively on their surface, thus triggering platelet adhesion and aggregation on vessel walls ⁽²⁰⁾. The most acknowledged theory that examined the association of CMV and APS demonstrates that acute CMV infection is associated with transient appearance of APL which has been documents *in vitro* ⁽²¹⁾ and *in vivo* ^(22, 23). Antiphospholipid syndrome is usually associated with the slowly produced thrombosis that cause hypertension and infraction of the placenta mainly in the third trimester of the pregnancy ⁽⁶⁾.

In the current study, the high seroprevalence of APL IgG among women with BOD post CMV infection (90% at 95% CI) along with the statistically significant correlation between seropositive APL-IgG and abortion ($P=0.04$) is in alignment to the previous studies^(5,6,7, 19) and it is suggestive for the necessity of the early diagnosis for APL at the earliest possible opportunity to apply the necessary measures and interventions which will minimize the risk of the predicted adverse pregnancy outcomes.

In the current study, the seroprevalence of APL IgG and IgM within the patient group (25.7%, 11.4%) was similar to an earlier study from Baghdad⁽²⁴⁾, where 27.12% and 15.1% prevalence rate were recorded for APL IgG and IgM respectively. This result was also in alignment to previous local studies from Iraq where seroprevalence of 20.63%, 26.5% were recorded for anticardiolipin for the patient group, respectively^(25, 26).

In our study, 100% of the 12 patients recorded with concurrent infections (CMV+ve + APL IgG and/or IgM +ve) were found to be aborted. The association between infection status whether single or concurrent and the pregnancy outcome was found to be significant at P value of 0.02. This might explain that APL IgG antibodies produced post CMV infection⁽²⁾ most probably will provoke the adverse pregnancy outcome. Despite the positive relation found, there is however no statistically significant association for the prevalence of APL IgG and IgM between patient and control group compared to a previous study RAZA et al., (2019)⁽²⁵⁾ where a significant correlation was found ($P<0.05$). The reason behind this might be attributed to the small number of the study population included in the present study. Further studies with larger population size might be of high importance to be screened and investigated to counteract such discrepancies and to obtain a wider picture for the association between APL syndrome and CMV infections.

In the current study, evidence of past and current infection of APL was highest amongst those who

had abortions (90%,100%), the educated for < 6 years (25.8%, 75%) and overcrowded (22.9%, 75%) for IgG and IgM, respectively. The significant correlation between APL-IgG and abortion proven in the current study is comparable to previous studies where a high prevalence of women with late fetal loss were APL-positive. In one of these Indian studies reported by Ghosh, (2006)⁽²⁷⁾, 27.7% of aborted women at a later stage of pregnancy were APL positive. Herrera (2017)⁽⁹⁾ reported that increased risk of fetal death is strongly related to positive APL tests compared to control group. In another study⁽²⁶⁾, 512 stillbirth cases were analysed from 2006 to 2008 and found that 11% of these women were seropositive for APL.

The seroprevalence of APL IgG and IgM among women with BOD recorded in our study population (90%, 100%) was higher than that reported by other studies⁽²⁸⁾; 27.7%, 11% respectively. The reason behind this might be attributed to the fact that in these two studies, women were mainly recruited based on a later stage of pregnancy loss (stillbirth) while in our study, aborted women were recruited from all three trimesters.

The non-significant statistical correlation between APL-IgM and abortion in our study is comparable to previous studies^(29, 25). IgM-type immunoglobulin is the largest species and therefore cannot cross the placenta from mother to fetus during pregnancy^[30,31]. As a result, immunoglobulin cannot induce abortion in women with anti-cardiolipin (IgM-ACL) and in turn supports our finding⁽²⁵⁾.

Similar to the results of APL, CMV IgG was highest among aborted (77%), educated for <6 years (85.7%), those living in overcrowded situations (91.4%). These results are in alignment with a previous study from Abbas and Egbe (2021) where seroprevalence of CMV was investigated in women of bad obstetric history⁽³²⁾.

In the current study, the prevalence of CMV IgG increased with the age and reached the peak (40%) at age 30-39, then it declined to 14.3% at age ≥ 40 . The seroprevalence of APL IgG among age

group were highest (31%) among patient aged 21-29 Yrs old. The ratio was then declined at age ≥ 30 . The figure for APL IgM was different from that of IgG, the peak (50%) was at age >30-39, then declined at ≥ 40 Yrs old to 0%. The results for the age group were not consistent with that of Raza et al., 2019⁽²⁴⁾ where the highest rate of anticardiolipin antibody was recorded within the age group from 36-45 Yrs old. This discrepancy might be attributed to several reasons including; the different age range used in that study, different sample size, or to the different levels of hormones of the study populations which is attributed to pregnancy, including Estrogen and Testosterone which is another factor influencing the immune system and thus might increase the susceptibility of women to viral infections⁽²⁶⁾.

Conclusion:

This is the first study into the association of APL and CMV infection amongst women with BOH in Al-Hamza district in Babil/Iraq. This study revealed a significant correlation between concurrent infection (CMV+ve & APL+ve) and abortion, this finding is in alignment with previous local studies from Iraq. This study emphasizes the necessity for seroprevalence data of APL post CMV infection for women with BOH in local populations to be researched and documented. The availability of these data will in turn, help in the planning and the implementation of demographically appropriate intervention programs that improve pregnancy outcome amongst APL seropositive women in Babil/ Iraq. Filling this gap is the purpose for this paper.

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