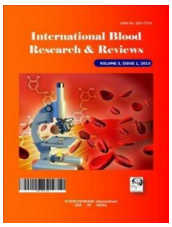

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Assessment of Some Key Haematological Parameters on Cytomegalovirus Antibody Positive Pregnant Women in Makurdi Nigeria

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Authors' contributions

This work was carried out by all the authors. Author OAM conceptualized, analyzed and prepared the manuscript for publication. Author OAT conducted the test and collected data while authors AOO and SIN wrote and proof read the manuscript for publication. All authors read and approved the final manuscript.

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ABSTRACT

Background: There is high prevalence of Cytomegalovirus (CMV) in pregnancy worldwide, primary infection in particular has been associated with significant haematological changes and childhood neurodevelopmental disabilities. There is however, paucity of information on the effect of CMV seropositivity in pregnancy on the haematological parameters of pregnant women from our centre.
Aim: This study was therefore designed to determine the effects of CMV sero-positivity among pregnant women, in Makurdi Nigeria, on some key haematological parameters.
Methods: A cross sectional study of 211 pregnant women aged 15-50 years attending antenatal clinic at The Benue State University Teaching Hospital & Federal Medical Centre, Makurdi, Nigeria, from November 2016 to April 2017 was conducted. They were screened & grouped based on their

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CMV status into three groups: The overall CMV status (irrespective of antibody type), CMV IgG status and CMV IgM status. Their Mean White Blood Count (WBC), Platelet Count, Absolute Neutrophil Count (ANC), Absolute Lymphocyte Count (ALC) and Haemoglobin (Hb) levels were estimated & compared. Data obtained were coded, entered and analysed with SPSS version 20. Simple proportion was used to determine CMV positivity. The independent sample t-test and Pearson's chi-square were used for comparison of quantitative variables and chi-square test for qualitative variables. Relationships were determined, and a P< .05 was considered significant.

Results: The younger pregnant women age 21-30 years constituted 75.4%, and represented the highest respondents. In those who were CMV IgG positive, WBC, platelets, ALC & haemoglobin all appeared lower & ANC appeared higher. In the CMV IgM positive, Haemoglobin & platelets appeared lower, while WBC, ANC & ALC all appeared higher. Overall, in those positive for CMV (irrespective of antibody type), WBC, platelet and haemoglobin appeared lower and ANC & ALC appearing higher. In all, these differences were not statistically significant, with P> .05

Conclusion: Cytomegalovirus seropositivity was found not to have any statistically significant effect on the haematological parameters of the pregnant women. We recommend further research in this area, education, and follow up on women with primary infection.

Keywords: Cytomegalovirus; immunoglobulin; pregnant women.

1. INTRODUCTION

Human Cytomegalovirus (HCMV) is a human herpesvirus type 5 (HHV-5), & belongs to the herpesviridae family [1].

New (primary) Cytomegalovirus (CMV) infection is common during childhood, consequently seroprevalence in the general human population is very high [2,3]. The prevalence of CMV infection ranges between 30%-90%, and the rate of infection increases with age [2]. One study in the United States documented a steady increase in CMV prevalence from 36.3% to 90.8% in 6–11-year-olds to 80 years old age groups respectively [3]. Important risk factors for CMV infection include age, geographic location and socioeconomic factors, other risk factors include blood transfusion, kissing, breastfeeding, sexual contact, solid organ and haemopoietic stem cell transplantation [2].

CMV is a highly pathogenic herpesviruses, Primary infection with the virus carries the highest chance of congenital infection & is associated with very high perinatal morbidity and mortality [2,4]. Congenital CMV infection is an important cause of neurodevelopmental abnormalities and the leading infectious cause of deafness in children [5,6].

CMV has also been associated with significant haematological changes referred to as CMV mononucleosis syndromes and cytomegalic inclusion diseases [7,8]. Some of these changes include reactive lymphocytosis, monocytosis and variable cytopaenias, especially thrombocytopaenia. Disseminated Intravascular Coagulation (DIC) has also been a feature of CMV Vireamias [7,8].

Following primary CMV infection in an immunocompetent person, the virus persists for years in a latent phase and may not lead to any clinically important illness, while in immune compromised individuals such as pregnant women, foetuses, HIV-infected hosts, organ transplant recipients and patients on immunosuppressive drugs, reactivation may occur years later [9,10].

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In the immunocompromised persons, both primary and reactivated (secondary) infections are associated with serious disease and complications. In pregnant women, the highest risk is with foetus and the new-borns [5,6]. The risk of symptomatic congenital infection is lower in a reactivated (secondary) than in primary CMV infection, this is because the maternal CMV antibodies present in the case of reactivated infection tend to prevent intrauterine transmission [6].

On CMV latency & reactivation, monocytes and macrophages have been implicated, suggesting that macrophages and their lineage cells provide a long-lived site for CMV latency [11,12]. The viral genome is carried and remained in the primitive hematopoietic mononuclear cells of the peripheral blood and bone marrow during latency and that reactivation occurs as the macrophage or dendritic lineage cells differentiate [11,12].

Maternal CMV infections are usually asymptomatic, and so diagnosis of maternal CMV infection is mostly via laboratory means, the diagnosis can either be by tissue culture viral isolation or by serologic technique [13]. The viral antigen in tissue culture (used to confirm diagnosis) can be identified & isolated within twenty hours by viral shell assay, immune-fluorescent staining, monoclonal antibody, and PCR techniques [13,14]. Evidence of maternal IgM seroconversion (i.e. in a previously negative person), is needed to confirm the diagnosis of a primary infection, however the use of maternal CMV IgM in the diagnosis of primary infection has some limitations; IgM antibodies can persist after primary infection for months to even years, it can also be seen in reinfection or in reactivation [13,15].

IgG antibody avidity can be used to differentiate acute recent from past infection, and this is based on the fact that avidity increases as immune response to a particular antigen matures over time, and that means that the more recent the infection, the less the avidity, while the less recent the infection the stronger the avidity [15]. Thus low avidity anti-CMV IgG early in pregnancy suggests a recent acute infection, and this can be used to know pregnant women at higher risk of foetal infection and complication, while high-avidity IgG antibodies up to 16 weeks of gestation signifies past infection, most likely before conception [15].

While routine CMV infection screening in pregnancy has not yet been recommended by CDC, educating pregnant women and women planning to get pregnant, about CMV prevention, has been recommended [16,17]. It was stated that this knowledge will help them to know how careful and cautious they must be to avoid getting infected [16,17]. Failure to recommend routine CMV screening was because of the difficulties of establishing diagnosis and the lack of effective therapy against CMV in pregnancy [16,17].

While some countries still view cytomegalovirus as a benign opportunistic pathogen that is not likely to produce any significant clinical infection, others like UK have already made attempts at two routine CMV screening [16,17]. In the UK, the first screening was antenatal, to detect women who acquire the infection in pregnancy and second was neonatal screening of the infant to detect infants with congenital infection who are at risk of adverse sequel, although this approach is still subject to periodic review [16,17].

At the time of this work, extensive literature search yielded no published work on the assessment of haematological parameters among CMV antibody positive pregnant women from our centre. This glaring information dearth necessitated this study. Again, Leukocytosis, physiological anaemia and gestational thrombocytopaenia from haemodilution are known common haematologic effects of many normal pregnancies [18], it would therefore be interesting to know whether or not, CMV infection & pregnancy exert combined effect on the haematological parameters. This study design therefore aimed to evaluate the effect CMV seropositivity on some major haematological indices among pregnant women seeking antenatal care at tertiary health care centres in Makurdi.

2. MATERIALS AND METHODS

This was a cross sectional study of pregnant women aged 15-50 years, attending antenatal clinic at The Benue State University Teaching Hospital & Federal Medical Centre, Makurdi, Nigeria, from November 2016 to April 2017. Two hundred and eleven (211) of them were selected through random sampling and grouped based on their CMV status into overall CMV status (irrespective of antibody type), CMV IgG status and CMV IgM status. Ethical approval was obtained from the research and ethical committee of Federal Medical Centre, Makurdi. Informed consent was obtained from all the participants. Relevant personal, social and demographic information were obtained with the aid of a pretested self-administered questionnaire. Non-consenting pregnant women were excluded from the study.

Six millilitres (6 ml) of venous blood was collected aseptically from each of the consenting pregnant women. Three (3) ml was dispensed into an ethylene diamine tetra acetic acid (EDTA) anticoagulant bottle which was analysed within 5 hours of collection, using an automated haematology analyser by Sysmex XN series. White cell count (WBC), Platelets count, Absolute Neutrophil Count (ANC), Absolute Lymphocyte Count (ALC) & haemoglobin (Hb) concentration were estimated. These tests were done according to manufacturer's instructions and the results were interpreted and documented accordingly. The remaining 3ml of whole blood was emptied into a sterile labelled plain vacutainer tube and was allowed to clot by standing at room temperature and then spun in a

centrifuge at 2500 g for 5 minutes to separate the serum. The sera were then dispensed into a cryovials and stored at –20°C until required for use. The sera were screened for CMV-IgG and CMV-IgM antibodies with Enzyme-Linked Immunosorbent Assay (ELISA) by Sekisui Verotech GmbH Löwenplatz 5 65428 Rüsselsheim Germany.

2.1 Virotech ELISA Test Procedures

Purified CMV antigen micro-wells were used. For each test run, 100µl each of dilution buffers (blank), IgG and IgM-positive, negative and cut-off controls (calibrator control) as well as diluted patient sera were pipetted.

Hundred (100)µl of these and Patient serum were added to the wells in duplicates, incubated for 30 min. at 37°C (with cover). All unbound materials were washed 4 times. Conjugate reagent was added into the washed test solution and then Incubated for 30 min. at 37°C (with cover). Excess conjugate was washed off and a solution of 3,3',5,5'-Tetramethylbenzidine (TMB) reagent was added and incubated for 30 min. at 37°C (with cover). Then 50µl of citrate stopping solution was added into each well. The plate was agitated carefully and thoroughly until liquid was completely mixed and a homogeneous yellow colour was visible.

Extinction (OD) was measured at 450/620 nm (Reference Wavelength 620-690 nm). The photometer was set such that the blank value was deducted from all other extinctions. Extinctions were measured within 1 hour after adding the stopping solution.

The intensity of the colour generated was propositional to the amount of IgG or IgM specific antibody in the sample. The results were read by a micro-well reader compared in a parallel manner with cut-off control (calibrator) and controls.

2.1.1 Test function control

a. OD-values

The conditions were that OD of the blank should be < 0.15. The OD-values of the negative controls were to be lower than the OD-values mentioned in the Quality Control Certificate. The OD-values of the positive controls as well as of the cut-off controls were to be above the OD-values mentioned in the Quality Control Certificate.

b. Virotech units (VE)

The Virotech Units (VE) of the cut-off controls were defined as 10 VE. The calculated VE of the positive controls were to be within the ranges mentioned in the Quality Control Certificate.

Where these requirements (OD-values, VE) were not fulfilled, the test was to be repeated.

2.1.1.1 Calculation of the Virotech Units (VE)

The extinction of the blank value (450/620 nm) was subtracted from all other extinctions.

VE (positive control) =OD (positive control)/ OD (cut-off control) x 10

VE (patient serum) = OD (patient serum)/OD (cut-off control) x 10

Interpretation Scheme IgG and IgM Result

Result (VE)	Evaluation
<9.0	Negative
9.0-11.0	Borderline
>11.0	Positive

1. When the measured values were above the defined borderline range, they were considered to be positive.
2. When the measured VE was within the borderline range, no significant high antibody concentration was present, the samples were considered to be borderline
3. When the measured values were below the defined borderline range, no measurable antigen specific antibodies were present in the samples. The samples were considered to be negative.

2.2 Data Analysis

Data obtained were coded, entered and analysed with SPSS (Statistical Package for the Social Sciences) version 20. The Means & standard deviation (SD), using ANOVA, were calculated for the haematological parameters. Simple proportion was used to determine CMV positivity. The independent sample t-test and Pearson's chi-square were used for comparison of quantitative variables and chi-square test for qualitative variables. Relationships were determined, and a $P< .05$ was considered significant.

3. RESULTS

3.1 Age and CMV Status of Respondents

Most of the 211 respondents attending antenatal clinics in our centre were young pregnant women, 159(75.4%), between 21-30 years of age, and the occurrence of CMV IgM, 1(12.5%) & 9(5.7%), seemed higher in the younger respondents, while CMV IgG, 8(100%) & 34(94.4%), seemed higher in the older women from 31-50 years of age (Table 1). The prevalence of CMV IgG was 94.3% and that of CMV IgM was 5.7% (Table 1).

3.2 Haematological Parameters & CMV IgG Status

WBC, platelets, ALC & haemoglobin all appeared lower & ANC appeared higher, these differences were however not statistically significant with *P*> *.05*. (Table 2).

3.3 Haematological Parameters & CMV IgM Status

Haemoglobin & platelets appeared lower in CMV IgM positive pregnant women, & WBC, ANC & ALC all appeared higher, the differences were also not significant, with *P*> *.05* (Table 3).

3.4 Haematological Parameters & Overall CMV Infection Status

This is irrespective of CMV antibody type. WBC, platelet and haemoglobin appeared lower and ANC & ALC appeared higher among the pregnant women who were CMV positive, the difference was also not statistically significant with *P*> .05 (Table 4).

Table 1. Age and CMV status of respondents

		Ig M	Ig G	Total (%)
		n(%)	n(%)	
Age (yrs)	15-20	1(12.5)	7 (87.5)	8(3.8)
	21-30	9(5.7)	150(94.3)	159(75.4)
	31-40	2(5.6)	34(94.4)	36(17.1)
	41-50	0(0.0)	8(100)	8(3.8)
Total		12(5.7)	199(94.3)	211(100)

Table 2. Haematological parameters & CMV IgG status

CMV IgG	n(%)	Haematological parameters				
		WBC(x10^9/L)	Plat(x10^9/L)	ANC(x10^9/L)	ALC(x10^9/L)	Hb(g/dl)
Pos	196(92.89)	6.71±1.27	221.49±56.61	9.21±3.17	2.13±0.60	11.03±0.69
Neg	15(7.11)	6.81±1.62	234.07±72.33	8.57±3.22	2.13±0.66	11.46±0.84
Total	211(100)	6.71±1.29	222.38±57.75	9.16 ±3.17	2.13± 0.60	11.06±0.71
	P -value	.127	.494	.900	.690	.194

Table 3. Haematological parameters & CMV IgM status

CMV IgM	n(%)	Haematological parameters				
		WBC(x10^9/L)	Platelets(x10^9 /L)	ANC(x10^9 /L)	ALC(x10^9 /L)	Hb(g/dl)
Pos	8(3.79)	6.75±1.07	188.63±60.24	9.91±2.11	2.35±0.31	10.87±0.75
Neg	203(96.21)	6.71±1.30	223.71±57.40	9.13±3.21	2.12±0.61	11.07±0.70
Total	211(100)	6.71±1.29	222.38±57.75	9.16 ±3.17	2.13± 0.60	11.06±0.71
	P -value	.848	.091	.491	.563	.309

Table 4. Haematological parameters & overall CMV infection status

CMV status	n(%)	Haematological parameters				
		WBC(x10^9/L)	Platelets(x10^9 /L)	ANC(x10^9 /L)	ALC(x10^9 /L)	Hb(g/dl)
Yes	197(93.36)	6.70±1.26	220.32±56.68	9.26±3.14	2.13±0.60	11.03±0.69
No	14(6.64)	6.85±1.69	251.36±66.91	7.86±3.47	2.11±0.63	11.52±0.83
Total	211(100)	6.71±1.29	222.38±57.75	9.16 ±3.17	2.13± 0.60	11.06±0.71
	P -value	.109	.095	.409	.764	.129

4. DISCUSSION

In a study on CMV prevalence, the highest number of respondents, attending antenatal clinics in their centre was that of younger pregnant women [2,19]. This is similar to our finding and can be explained by the fact that the studies were done in the same geographic region with similar socio-cultural practices and religious believe. These factors support and promote early marriages and putting younger girls in the family way very early in life.

Some studies from the region, reported higher occurrence of CMV IgM in their younger pregnant women and CMV IgG in the older pregnant women [2]. This again, is in agreement with our finding. This showed that more of the younger pregnant women had primary CMV infections, probably because they were exposed for the first time, had recent infection. Many may have had their first one or two pregnancies and getting exposed to smaller children and other risk factors for CMV infection. This also showed that the older pregnant women have been exposed much earlier and had old infections. There were few other studies that reported lack of association between age and CMV antibody types [20].

This finding has some implications, for example, the younger ones with recent or reactivated infections are more at risk of developing perinatal complications of CMV infection, either haematological or foetal. This also justified the need for this study, and calls for follow up and close monitoring of these women for onset and early detection of any haematological complication. In the older women, because of the existing predominant IgG antibodies, they are better protected from the perinatal and other haematological complications than the younger pregnant women with CMV IgM.

The high prevalence of 94.3% for CMV IgG in our study is also worrisome, and this is the case with many of the studies from the region [19,21].

A study from Netherland reported CMV infection as a significant cause of delay platelet recovery after Bone Marrow Transplantation (BMT) [22]. The CMV positive group of patients had a significantly slower platelet & granulocyte recovery compared to the CMV negative group. This demonstrated a significant negative effect of cytomegalovirus infection on platelet and granulocytes. This study finding was however at variance with our findings. This may be explained by the difference in the study population groups, they used patients with already primary bone marrow diseases while we used apparently healthy pregnant women. Even though both conditions have the potentials to induce thrombocytopaenia, gestational & CMV induced thrombocytopaenia are more likely to be less significant.

Similarly, in one case report, cytomegalovirus infection was reported to have caused cytomegalovirus induced severe thrombocytopaenia in a male patient [23]. Again this finding was in variance with ours, and may still be explained by the variation in study subjects.

In another study, it was stated that some haematological parameters “suggestive of CMV infection include a differential white blood cell (WBC) count showing atypical lymphocytes and a low platelet count” [13].

Overall, most of the studies reviewed documented low platelet in CMV positive pregnant women and variable effects of CMV on granulocytes and lymphocytes. Even though our study showed a similar pattern, with the overall effect of CMV infection (irrespective of antibody type), as lower platelet, haemoglobin & total WBC and higher neutrophil and lymphocytes, the findings were however not statistically significant.

5. CONCLUSION

Though, our study showed an apparent negative effect of CMV on the haematological parameters, this however was of no statistical significance.

We recommend further research in this subject area, institution of routine education of pregnant women and women preparing to get pregnant, on CMV infection prevention, counselling them on the importance of careful hand hygiene practices, especially those exposed to young children, in order to decrease the risk of primary CMV infection with the attendant complications.

There is also a need for follow up on pregnant women with high CMV IgM antibodies or evidence of recent or primary infection, for early detection of any haematologic complication.

6. LIMITATION OF THIS STUDY

During the study period, intense literature search yielded extremely low previous work on this

topic, and so there was paucity of information on the effect of cytomegalovirus seropositivity on the haematological parameters of pregnant women. Most of the cases found were on other study subjects, mostly men and non-pregnant women.

The second limitation was our inability to carry out CMV IgG avidity test that would have been a better indication or otherwise of recent or primary infection.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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