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# Comparative Study of Serum Immunoglobulin Levels in Healthy HIV Sero-Negative Non-Pregnant Subjects, Hiv Sero-Positive Pregnant Subjects and Subjects with Malaria Infection During Pregnancy in Port Harcourt, Nigeria

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**Abstract:** The present study aims to determine levels of IgA, IgG and IgM in HIV sero-negative pregnant subjects, subjects with malaria infection during pregnancy and HIV sero-positive pregnant subjects as compared to healthy HIV sero-negative non-pregnant subjects in Port Harcourt, Nigeria. This is to enable better understanding of the pattern of changes of immunoglobulin concentration in malaria and HIV infection and assist in the antenatal management of these subjects in our environment. A total of 200 female subjects resident in Port-Harcourt, southeastern Nigeria were recruited into the study. These comprised four groupsof 50 female subjects in each group: healthy HIV sero-negative, non-pregnant subjects (group A); healthy HIV sero-negative pregnant subjects (group B); subjects with malaria infection during pregnancy (group C) and HIV sero-positive pregnant subjects (group D). All pregnant subjectswere further divided to the appropriate trimester depending on the duration of their pregnancy. Venous blood samples were obtained and levels of immunoglobulins A, G and M determined with the turbidimetric immunoassay method using an automated chemical analyzer. Significant differences were observed in the values of the various types of immunoglobulins studied between healthy HIV sero-negative non-pregnant (group A) subjects and healthy HIV sero negative pregnant (group B) subjects. Noteworthy is the observation that the values of both IgG and IgM were significantly higher while the values of IgA were significantly lower amongst the non-pregnant subjects in group A, compared to all the other pregnant subject groups: B, C and D ($p<0.05$). Furthermore, group B subjects were found to have significantly higher values of both IgG and IgM compared to group C subjects but significantly lower values compared to group D subjects ($p<0.05$). Values of IgA were found to be consistently higher in both group C and D subjects as compared to both group A and group B subjects. During the course of gestation, both group C and D subjects were found to have significantly higher values of IgA compared to group B subjects ($p<0.05$); whereas group C subjects were found to have significantly lower values of both IgG and IgM compared to group B subjects ($p<0.05$). Group D subjects were found to have significantly higher values of both IgG and IgM compared to group B subjects ($p<0.05$). These differences were found to exist despite the duration of gestation. The present study reports that IgG and IgM values were significantly lower and IgA values significant higher in all pregnant subjects compared to HIV sero-negative non-pregnant subjects. Furthermore, in subjects with malaria in pregnancy IgG and IgM levels were consistently and significantly low and IgA levels were found to be lowest amongst HIV sero-negative pregnant subjects. Our study describes for the first time the pattern of these changes in immunoglobulin values amongst pregnant subjects of southeastern Nigeria and confirms previous suggestions of an apparent modulation of the immune system by the effects of both pregnancy and malaria infection during pregnancy. We recommend the continual need for adequate checks and enhanced care of these subjects by antenatal care providers in southeastern Nigeria.

**Key words:** Malaria, HIV, immunoglobulin, pregnancy, women, immunity

## INTRODUCTION

Amongst residents of endemic areas, especially pregnant women and children under age five, malaria infection induces strong humoral immuneresponses involving theproductionofpredominantlyIgMandIgGas well as other immunoglobulin isotypes (Perlmann and Troye-Blomberg, 2002) Studies on serum immunoglobulin

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levels in pregnancy have shown varying results.In one studyof normal gestation in Nigerian women, IgG and IgMlevels were found to decline progressively with significant decreases between the first and second trimesters and a further significant decrease between the second and third trimester. No differences were observed for IgA levels through normal pregnancy (Ogbimi and Omu, 1989), 3However (Khirwadkar and Kher, 1991) reported decreasesin the concentration of both IgG and IgAand increases in IgM with increasing gestation amongst Indian women. In pregnant Caucasian women, Miller and Abel (1983) described an initial rise in both IgG and IgA levels and later a decrease after week 17 with no differences in IgA levels from week 20 as compared to non-pregnant controls. These reports suggest immense variability in the pattern of changes of immunoglobulin values in the physiologic state of pregnancy. Indeed, suppression of the maternal immune response is one of the likely factors contributing to the continuation of pregnancy; a state in which the fetus exists as a well-tolerated homograft (Khirwadkar and Kher, 1991).

Malaria and HIV infections have beenreported to be among the most important global health problems confronting developing countries: causing an estimated 4 million deaths annually. Pregnant women particularly, suffer serious consequences when co-infected with malaria and HIV (Alemu *et al*., 2013). In pregnant subjects, co-infection with HIV can increase the adverse effects of malaria including anemia and placental malaria infection (Ayisi *et al*., 2003). Further, not only has HIVinfection been reported to adversely affect the acute antibody response to malaria antigens in both children and pregnant women; several studiesdescribe a possible deleteriouseffect on the immune system (Alemu *et al*., 2013; Bunders *et al*., 2010; Muema *et al*., 2011). Immune functions in pregnancy is further suppressed in HIV sero-positive women with a decrease in immunoglobulin values, reduced complement levels in early pregnancy and more significantly, a decrease in cell-mediated immunity (Bunders *et al*., 2010; Muema *et al*., 2011). These changes during the course of pregnancy have led to concern that the effect of pregnancy in HIV infection could be to accelerate the progression of infection (Alemu *et al*., 2013). However, no statistically significant correlation has been described between HIV viral load and levels of serum immunoglobulin in HIV sero-positive Nigerian mothers (Akinpelu *et al*., 2012). Conversely in Nigerian subjects, HIV infection is known to impairB lymphocyte function and is associated with increased immunoglobulin levels especially,amongst HIV-infected pregnant women (Miotti *et al*., 1992). Such increase in immunoglobulin levels may not lead to a safe healthy pregnancy outcome. Indeed, adverse pregnancyoutcomes havebeen commonlyreported in a number of African studies (Miotti *et al*., 1992) withcomplications reported in both earlyandlate pregnancy (Temmerman *et al*., 1994; D'Ubaldo *et al*., 1998).

Studies on immunological parameters including immunoglobulins levelsin pregnant subjects have been relatively scanty especially from Southeastern Nigeria. Previous studies from our centerhave focused at establishing normative values and reference ranges for various haemorheological and some immunological parameters amongst children (Dapper *et al*., 2009; Obiandu *et al*., 2013) healthy adults (Obiandu *et al*., 2013; Dapper *et al*., 2008). Healthy pregnant subjects (Amah-Tariah, 2011) and amongst pregnant subjects with pre-eclampsia (Okerengwo *et al*., 1990) Considering reported adverse effects of malaria and HIV infection in pregnancy the present study aims to determine levels of IgA, IgG and IgM in HIV sero-negative pregnant subjects, subjects with malaria infection during pregnancy and HIV sero-positive pregnant subjects as compared to healthy HIV sero-negative non-pregnant subjects in Port Harcourt, Nigeria. This is to enable better understanding of the pattern of changes of immunoglobulin concentration in malaria and HIV infection and assist in the management of these subjects in our environment.

## MATERIALS AND METHODS

**Subjects:** A total of 200 female subjectsaged between 18 and 40 year were randomly recruited from amongst patients attending the ante-natal and general out-patient clinics of a number of primary, secondary and tertiary health care institutions in Port Harcourt, Nigeria. Healthy non pregnant HIV sero-negative female staff of these institutions were also recruited as controls. Subjects were of various socio-economic classes and ethnic groups resident in southeastern Nigeria. No subject had any co-existing abnormality and none had previously received any form of blood transfusion. The subjects were divided into 4 groups with each group consisting of 50 subjects:

- Group A: healthy HIV sero-negative, non-pregnant subjects
- Group B: healthyHIV sero-negative pregnant subjects
- Group C: subjects withmalariainfection during pregnancy and
- Group D: HIV sero-positivepregnant subjects

All pregnant subjects, comprising of subjects in Groups B, C and D were further divided into three subgroups: first, second and third trimester, depending on

their duration of pregnancy. For the present study, the first trimester was considered to end at the 13th week, the second trimester to end at the 26th week and the third trimester to end at 40 weeks (Amah-Tariah, 2014). Ethical approval for the study was obtained from our institutional ethics committee and informed consent obtained from each subject prior to recruitment into the study.

**Blood collection:** The 5 mL of venous bloodwas carefully collected from an ante-cubital vein with the subject comfortably seated and with minimal stasis. The blood was transferred into anticoagulant free sample bottlesappropriately labelled andallowed to coagulate. The samples were centrifuged, serum obtained and stored at -20°C until ready for immunoglobulin assay. All assays were done within two weeks of blood collection.

**Assay of immunoglobulin levels:** Serum levels of immunoglobulins A, G and M was determined using the immunoturbidimetric assay method with a fully smart automated clinical chemistry analyzer (Biochemical Systems International Srl, Italy), Clindiag system B.V.B.A immunoglobulin reagent kits and immunoglobulins A, G and M kits (Belgium, Germany).

**Immunoturbidimetric method:** The principle of immunoturbidimetric method involves determination of immunoglobulin concentration through photometric measurement of immune complexes between antibodies of immunoglobulin and immunoglobulin present in the samples, the absorbency of which is directly proportional to the concentration of the immunoglobulin.

Preparation of reagent was done using the serum start method: the Clindiag reagent components, R1 (100mmol $L^{-1}$ Tris butter, 50 g LPEG6000) and R2 (100mmol $L^{-1}$ Tris butter, 50 g L PEG 6000, anti-immunoglobulin antibody) were mixed in a ratio of 3:1 to produce a working solution which was dispensed into appropriately labelled reagent bottles and placed in the automated analyser's reagent tray. Diluent bottles were filled with distilled water. Blood samples were subsequently thawed and labelled appropriately. Assay procedure was programmed on fully smart chemistry analyser using multi standard programmes method and test identification was entered for IgA, IgG and IgM. Assay conditions were set accordingly: The 340 and 670 nm main wavelength and sub-wavelength respectively, 37°C temperature, cuvette light path of 1.0 cm and absorbance range of 0-0.25A. Samples were dispensed into analyser's sample cups using automatic micropipette and placed in appropriate positions in the analyser's sample tray. Calibrations were made at manufacturer's specifications for automated chemistry analyser: IgA-4.5 $gL^{-1}$, IgG-26 $gL^{-1}$ and IgM-2.5 $gL^{-1}$. A graph of absorbance versus concentration for each standard was plotted to obtain a standard calibration curve which was used to determine immunoglobulin concentration.

**Statistical analysis:** The results obtained were presented in Table 1 and 2. All values are presented as mean ± standard deviation. Significant differences in the values of immunoglobulins isotypes between groups were determined using ANOVA. A $p<0.05$ was considered significant.

## RESULTS AND DISCUSSION

Table 1 shows the values of the various immunoglobulin types obtained for all subjects involved in the present study. Significant differences were observed in the values between healthy HIV seronegative non-pregnant (group A) subjects and healthy HIV sero-negative pregnant (group B)subjects. For instance, the value of IgG and IgM amongst group A subjects was 3615.92+261.50 and 238.68+38.38 mg $dL^{-1}$ respectively, these were found to significantly higher than the corresponding values amongst group B subjects which were: 1529.00+88.11 and 136.20+23.89 mg $dL^{-1}$ for IgG and IgM, respectively; while values of IgA for group B subjects found to be 130.24+14.0 mg $dL^{1}$ was significantly higher than the corresponding value amongst group A subjects found to be 119.76+16.794 mg $dL^{-1}$ ($p<0.05$). Noteworthy is the observation that the values of both IgG and IgM were significantly higher while the values of IgA were significantly lower amongst thenon-pregnant subjects in group A compared to all the other pregnant subject groupsin B, C and D($p<0.05$). For instance, the meanIgG and IgM values in group C (subjects with malaria infection during pregnancy) were found to be 1437.50+169.77 mg $dL^{-1}$ for IgG and 89.10+32.70 mg $dL^{-1}$ for IgM, respectively and in group D (HIV sero-positivepregnant subjects) were found to be 1694.00+170.79 mg $dL^{-1}$ for IgG and162.40+34.41 mg $dL^{-1}$ for IgM, respectively; these values were significantly lower thanthe corresponding values for Group A (healthy HIV sero-negative non-pregnant subjects) which were found to be: 3615.92+261.50 mg $dl^{-1}$ for IgG and 238.68+38.38 mg $dL^{-1}$ for IgM, respectively ($p<0.05$); however values of IgA were found to be significantly higher in groups B, C and group D subjects compared to group A subjects ($p<0.05$). Furthermore, group B subjects were found to have significantly higher values of both IgG and IgM compared to group C subjects but significantly lower values compared to group D subjects

Table 1: Values of the various immunoglobulin types obtained forall subjects

| Subject groups (n = 50) | ImmunoglobulinA (mg $dL^{-1}$) | ImmunoglobulinG (mg $dL^{-1}$) | ImmunoglobulinM (mg $dL^{-1}$) |
|---|---|---|---|
| Group A: Healthy HIV sero-negative, non-pregnant subjects | 119.76+16.794 | 3615.92+261.50 | 238.68+38.38 |
| Group B: HealthyHIV sero-negative pregnant subjects | 130.24+14.0[(a)] | 1529.00+88.11[(a)] | 136.20+23.89[(a)] |
| Group C: Subjects with malaria infection during pregnancy | 142.0+25.79*[(a)] | 1437.50+169.77*[(a)] | 89.10+32.70*[(a)] |
| Group D: HIV sero-positivepregnant subjects | 141.10+18.98*[(a)] | 1694.00+170.79*[(a)] | 162.40+34.41*[(a)] |

All values presented as Mean±SD; *Values are significantly different compared to Group B subjects; [(a)]Values are significantly different compared to Group A subjects

Table 2: Values of immunoglobulin A (IgA) obtained in the various trimesters of pregnancy amongst pregnant subjects

| Groups | First trimester (mg $dL^{-1}$) | Second trimester (mg $dL^{-1}$) | Third trimester mg $dL^{-1}$) |
|---|---|---|---|
| Group B: Healthy HIV sero-negative pregnant subjects (n = 50) | 133.30+29.02 | 130.08+16.20 | 128.05+18.01 |
| Group C: Subjects with malaria infection during pregnancy (n = 50) | 141.26+32.41* | 140.73+80.27* | 142.26+30.23* |
| Group D: HIV sero-positive pregnant subjects (n = 50) | 146.78+12.56* | 142.91+20.03* | 139.40+15.18* |

Table 3: Values of immunoglobulin G (IgG) obtained in the various trimesters of pregnancy amongst pregnant subjects

| Groups | First trimester (mg $dL^{-1}$) | Second trimester (mg $dL^{-1}$) | Third trimester (mg $dL^{-1}$) |
|---|---|---|---|
| Group B: Healthy HIV sero-negative pregnant subjects (n = 50) | 1519.87+54.00 | 1490.07+75.03 | 1488.22+21.50 |
| Group C: Subjects with malaria infection during pregnancy (n = 50) | 1431.81+118.13* | 1420.35+124.60* | 1445.82+102.34* |
| Group D: HIV sero-positive pregnant subjects (n = 50) | 1678.10+168.25* | 1795.30+120.57* | 1810.50+190.32* |

Table 4: Values of immunoglobulin M (IgM) obtained in the various trimesters of pregnancy amongst pregnant subjects

| Groups | First trimester (mg $dL^{-1}$) | Second trimester (mg $dL^{-1}$) | Third trimester (mg $dL^{-1}$) |
|---|---|---|---|
| Group B: Healthy HIV sero-negative pregnant subjects (n = 50) | 135.57+25.02 | 132.20+85.00 | 129.89+40.10 |
| Group C: Subjects with malaria infection during pregnancy (n = 50) | 95.13+33.40* | 89.27+17.13* | 81.48+24.60* |
| Group D: HIV sero-positive pregnant subjects (n = 50) | 165.19+60.08* | 169.38+27.63* | 172.53+41.33* |

Values presented as Mean±SD; *Mean values are significant different compared to Group B subjects

($p<0.05$). Values of IgA were found to be consistently higher in both group C and group D subjects as compared to both group A and group B subjects. Values of these immunoglobulin types are as shown in Table 1.

Table 2 shows the values of immunoglobulin A (IgA) obtained at the various trimesters of pregnancy amongst all the pregnant subjects of groups B, C and D. All through the course of gestation, both group C and group D subjects were found to have significantly higher values of IgA compared to group B subjects ($p<0.05$). Table 3 and 4 show values of immunoglobulin G (IgG) and immunoglobulin M (IgM) respectively obtained at the various trimesters of pregnancy amongst all the pregnant subjects of groups B, C and D. All through the course of pregnancy, whereas group C subjects were also found to have significantly lower values of both IgG and IgM compared to group B subjects ($p<0.05$); group D subjects were found to have significantly higher values of both IgG and IgM compared to group B subjects ($p<0.05$): these differences were found to persist despite the duration of pregnancy. Values of the various immunoglobulin types as obtained during the course of pregnancy in all our pregnant subjects are as shown in Table 2-4.

The present cross-sectional study aims at determining possible variations in the various immunoglobulin isotypes in healthy HIV sero-negative pregnant subjects, subjects with malaria infection during pregnancy and HIV sero-positive pregnant subjects as compared to healthy HIV sero-negative, non-pregnant (control)subjects in Port Harcourt, Nigeria. This is to enhance understanding of the pattern of immunoglobulin changes during pregnancy and in malaria and HIV infection. This may help determine possible regional and geographical differences and thus enhance the management of these conditions in the ante natal period in our environment (Bunders *et al*., 2010; Akinpelu *et al*., 2012; Miotti *et al*., 1992).

Expectedly, the mean levels of the most abundant immunoglobulin isotypes: IgG and IgM were found to be significantly and consistently lower in all pregnant subjects as compared to healthy HIV sero-negative but non-pregnant subjects (Group A); on the other hand, IgA levelwere found to be significantly higher amongst all the pregnant subject groups as compared to healthy HIV sero-negativenon-pregnant subjects (Group A). These findings are generally consistent with reports that during pregnancy the maternal immune system undergoes changes aimed at providing protection for the placenta and growing fetus (Malek, 2013). The findings are consistent with the report of Miller and Abel (1984) and WHO (2005) describes a rapid rise in immunoglobulin levels after delivery amongst Caucasian women. Our findings are also consistent with the report of Ogbimi and Omu (1989) amongst Nigerianwomen during normal pregnancy. However, Lafi *et al*. (2011) reports an increased value of both IgG and IgM levels in pregnant Egyptian women with an enhanced IgGplacental transfer during late pregnancy.

Noteworthy is the finding in the present study that during the course of gestation both IgG and IgM levels were consistently and significantly lowest amongst subjects with malariain fection; by contrast, the levels of IgA level were lowest amongst healthy HIV sero-negative pregnant subjects: confirming suggestions of an apparent modulation of the immune system by the effects of both pregnancy and malaria infection during pregnancy. Furthermore, amongst Group C subjects all the immunoglobulin isotypes studied showed an initial second trimester decrease followed by an increase in the third trimester (except IgM values which were found to persistently decrease) beyond values observed in the first trimester. Perhaps, these observed pattern may be due to the effects of malaria infection which is known to elicit intense immune responses (Martin and Hall 2000; Lawn *et al*., 2001) Reports indicate that malaria infection is associated with CD4+cell activation and up-regulation of pro inflammatory cytokines (WHO, 2005) both important for effective response of B-lymphocytes (responsible for immunoglobulin production) and cytotoxicT-lymphocytes (CD8+) (Janssen *et al*., 2003) Malaria infection is known to further induce apoptosis in patients with acute as well as chronic asymptomatic Plasmodium falciparum infection. This parasite-induced apoptosis would contribute to reducing the immune response towards critical antigens by increasing the fragility of potential effector cells (Toure, 1996; Alemu *et al*., 2013). Possibly, the significantly increased IgA level seen amongst all the pregnant subject groups in the present study may be due to the effects of pregnancy. This may perhaps be directly linked to the activation and up-regulation of pro-inflammatory cytokines which in turn, may possibly activate the respective B lymphocytes leading to increased IgA concentrations.

The persistent increase seen in the levels of both IgG and IgM during the course of gestation amongst HIV sero-positive pregnant subjects in the present study suggests polyclonal B-Cell activation with advancing disease with an enhanced B-cell response; apparently suggesting a possible direct immune stimulation by the HIV virus. This finding is not consistent with the report of Akinpelu *et al.,* 2012, who observed a decrease in immunoglobulin levels during healthy pregnancy and further found no statistically significant correlation between viral load and serum immunoglobulin levels of HIV sero-positive mothers. However, it has been suggested that observed possible differences between studies on maternal immunologic changes and the complex relationships between maternal immune response to malaria and or HIV infections may indeed depend on the severity of malaria and the degree ofHIV induced immuno suppression when the study was conducted. (Ter Kuile, 2004). Indeed, an increased susceptibility of HIV-infected pregnant women to malaria infection may perhaps be the result of modifications of systemic and placental immunologic parameters (Ter Kuile, 2004) Although, the suppression of maternal immune sensitivity during pregnancy is to preventfetal allograft rejection (Lafi *et al*., 2011) studies have revealed a further though partial impairment of humoral immune response to malaria in HIV-infected pregnant women (Ayisi *et al*., 2003). HIV infection induced impairment of malarial immunity is greatest in the most immunosuppressed women and could explain the increased susceptibilityto malaria seen in pregnant women with HIV infection.

## CONCLUSION

In conclusion, the present study reports that IgG and IgM values were significant lower and IgA values were significant higher in all pregnant subjects compared to HIV sero-negative non-pregnant subjects. Furthermore, we also report that in subjects with malariain pregnancy IgG and IgM levels were consistently and significantly low and amongst HIVsero-negative pregnant subjects IgA levels were found to be lowest. Our study describes for the first time the pattern of these changes amongst subjects of southeastern Nigeria and confirms suggestions of an apparent modulation of the immune system by the effects of both pregnancy and malaria infection during pregnancy. We recommend the continual need for adequate checks and increased care of these subjects in our environment amongst antenatal care providers.

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