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# Comparative study of Serum Immunoglobulin levels in Healthy Pregnant and Pregnant Subjects with HIV and Malaria Infection in Port Harcourt, Nigeria

**Amah-Tariah F.S.*, Bekinbo M.T. and Dapper D.V.**
Department of Human Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, University of Port Harcourt, PMB 5323, Port Harcourt, Nigeria
fortune.amah-tariah@uniport.edu.ng

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## Abstract

*The present study aims to determine IgA, IgG and IgM concentrations in healthy pregnant subjects, subjects with malaria and HIV infection during pregnancy as compared to healthy HIV sero-negative non-pregnant subjects in Port Harcourt, Nigeria. The study is purposed 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. In all, 200 female subjects in Port-Harcourt, southeastern Nigeria were incorporated into the study. These comprised four groups of 50 female subjects in each group: healthy HIV non-pregnant subjects (group A); healthy HIV pregnant subjects (group B); subjects with malaria infection during pregnancy (group C) and; HIV sero-positive pregnant subjects (group D). All pregnant women were 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. Statically significant differences were observed in the values of the various immunoglobuliniso types studied between healthy HIV non-pregnant (group A) subjects and healthy HIV pregnant (group B) subjects. Noteworthy is the observation that the mean 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, the healthy pregnant subjects (B) had significantly higher values of both IgG and IgM compared to group C subjects, but significantly lower values compared to group D subjects ($p<0.05$). Mean IgA values were found to be consistently higher in both pregnant malaria (C) and HIV (D) groups as compared to both groups A and group B subjects. During the course of gestation, both groups C and D subjects were observed to have significantly higher values of IgA compared to group B women ($p<0.05$); whereas group C subjects had markedly lower values of both IgG and IgM compared to group B subjects ($p<0.05$). Group D subjects were also observed to have significantly higher values of both IgG and IgM relative to group B subjects ($p<0.05$). These differences were found to exist despite the duration of gestation. This study reports that IgG and IgM levels were significantly lower and IgA values significantly increased in the pregnant subjects compared to the non-pregnant subjects. Furthermore, in subjects with malaria in pregnancy IgG and IgM levels were consistently and significantly low and IgA levels being the lowest amongst the healthy 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.*

**Keywords:** Malaria, HIV, Immunoglobulin, Pregnancy, Women, Immunity.

## Introduction

Amongst residents of endemic areas, especially pregnant women and children under age five, malaria infection elicits strong humoral immune responses that involve the production of predominantly IgM and IgG as well as other immunoglobulin isotypes[1]. Studies on serum immunoglobulin levels in pregnancy have shown varying results. In one study of normal gestation in Nigerian women, IgG and IgM levels 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[2]. No differences were observed for IgA levels through normal pregnancy[2,3]. However, Khirwadkar and Kher[4] reported decreases in the concentration of both IgG and IgA and increases in IgM with increasing gestation amongst Indian women. In pregnant Caucasian women, Miller and Abel[5] 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[4].

Malaria and HIV infections have been found to be amongst the most important global health issues confronting developing countries: causing an estimated 4 million deaths annually. In particular, pregnant women suffer serious complications when co-infected with malaria and HIV[6]. Co-infection with HIV exacerbates the adverse effects of malaria in pregnancy, including anemia and placental malaria infection[7]. Further, not only has HIV infection been reported to adversely affect the acute humoral response to malaria antigens in pregnant women; several studies describe a possible deleterious effect on the immune system[6,8,9]. Immune functions in pregnancy is further suppressed in HIV sero-positive women with a fall in immunoglobulin values, decreased complement levels in early pregnancy and more significantly, blunting of cell-mediated immunity[8,9]. These changes during the course of pregnancy have led to the belief that the effect of pregnancy in HIV infection could be to advance the severity of infection[6]. However, some studies reported that HIV viral load and serum immunoglobulin concentrations have no statistically significant correlation in HIV sero-positive Nigerian mothers[10]. Conversely in Nigerian subjects, HIV infection is known to impair B lymphocyte activity with a resultant increase in immunoglobulin levels especially, amongst HIV-infected pregnant women[10]. Such increase in immunoglobulin levels may not lead to a safe healthy pregnancy outcome. Indeed, adverse pregnancy outcomes have been commonly reported in a number of African studies[11] with complications reported in both early and late pregnancy[12,13].

Studies on immunological parameters including immunoglobulin levels in pregnant subjects have been parsimonious especially around Southeastern Nigeria. Previous researches from our center have been aimed at providing normative values and reference figures for different haemorheological and some immunological profiles amongst children[14, 15] healthy adults[15,16] healthy pregnant subjects[17] and amongst pregnant subjects with pre-eclampsia[18]. Considering reported adverse effects of malaria and HIV infection in pregnancy, this study aims to determine levels of IgA, IgG and IgM in healthy pregnant subjects, subjects with malaria infection during pregnancy and HIV sero-positive pregnant subjects as compared to healthy non-pregnant subjects in Port Harcourt, Nigeria, so as 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 subjects aged between 18 and 40 years 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: i. Group A: healthy HIV sero-negative, non-pregnant subjects, ii. Group B: healthy HIV sero-negative pregnant subjects, iii. Group C: subjects with malaria infection during pregnancy and; iv. Group D: HIV sero-positive pregnant 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 thirteenth week, the second trimester to end at the twenty-sixth week and the third trimester to end at forty weeks[17]. 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:** 5ml of venous blood was carefully collected from an ante-cubital vein with the subject comfortably seated and with minimal stasis. The blood was transferred into anticoagulant free sample bottles appropriately labelled and allowed to coagulate. The samples were centrifuged, serum obtained and stored at -20$^{o}$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 Tris butter, 50g/LPEG6000) and R2 (100mmol/L Tris butter, 50g/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: 340nm and 670nm main wavelength and sub-wavelength respectively, 37°C temperature, cuvette light path of 1.0cm 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- 4.5g/L, IgG- 26g/L and IgM- 2.5g/L.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 Tables 1 and 2. All values are presented as mean ± standard deviation. Significant differences in the values of immunoglobulinsiso types 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 sero-negative 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±261.50mg/dl and 238.68±38.38mg/dl respectively, these were found to significantly higher than the corresponding values amongst group B subjects which were: 1529.00±88.11 mg/dl and 136.20±23.89 mg/dl for IgG and IgM respectively; while values of IgA for group B subjects found to be 130.24±14.0mg/dl was significantly higher than the corresponding value amongst group A subjects found to be 119.76±16.794 mg/dl ($p<0.05$). Noteworthy is the observation that the values of both IgG and IgM were significantly higher while the values of IgA were significantly lower amongst then on-pregnant subjects in group A compared to all the other pregnant subject groups in B, C and D($p<0.05$). For instance, the mean IgG and IgM values in group C (subjects with malaria infection during pregnancy) were found to be 1437.50±169.77 mg/dl for IgG and 89.10±32.70mg/dl for IgM respectively and in group D (HIV sero-positive pregnant subjects) were found to be 1694.00±170.79mg/dl for IgG and162.40±34.41mg/dl for IgM respectively; these values were significantly lower than the corresponding values for Group A (healthy HIV sero-negative non-pregnant subjects) which were found to be: 3615.92±261.50mg/dl for IgG and 238.68±38.38mg/dl 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 ($p<0.05$). 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-2a 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-2b and Table-2c 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.

**Table-1**
**Values of the various immunoglobulin types obtained for all subjects**

| Subject groups | Immunoglobulin A (mg/dl) | Immunoglobulin G (mg/dl) | Immunoglobulin M (mg/dl) |
|---|---|---|---|
| Group A: Healthy HIV sero-negative, non-pregnant subjects (n=50) | 119.76±16.794 | 3615.92 ± 261.50 | 238.68 ± 38.38 |
| Group B: Healthy HIV sero-negative pregnant subjects (n=50) | 130.24 ± 14.0 [(a)] | 1529.00 ± 88.11 [(a)] | 136.20 ± 23.89 [(a)] |
| Group C: Subjects with malaria infection during pregnancy (n=50) | 142.0 ± 25.79*[(a)] | 1437.50 ± 169.77*[(a)] | 89.10 ± 32.70*[(a)] |
| Group D: HIV sero-positive pregnant subjects (n=50) | 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-2a**
**Values of immunoglobulin A (IgA) obtained in the various trimesters of pregnancy amongst pregnant subjects**

| Groups | First trimester (mg/dl) | Second trimester (mg/dl) | Third trimester (mg/dl) |
|---|---|---|---|
| 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* |

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

**Table-2b**
**Values of immunoglobulin G (IgG) obtained in the various trimesters of pregnancy amongst pregnant subjects**

| Groups | First trimester (mg/dl) | Second trimester (mg/dl) | Third trimester (mg/dl) |
|---|---|---|---|
| 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* |

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

**Table-2c**
**Values of immunoglobulin M (IgM) obtained in the various trimesters of pregnancy amongst pregnant subjects**

| Groups | First trimester (mg/dl) | Second trimester (mg/dl) | Third trimester (mg/dl) |
|---|---|---|---|
| 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.

**Discussion:** 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[3,8,10].

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 level were found to be significantly higher amongst all the pregnant subject groups as compared to healthy HIV sero-negativen on-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[19]. Our findings are consistent with the report of Miller and Abel[5] who describes a rapid rise in immunoglobulin levels after delivery amongst Caucasian women. Our findings are also consistent with the report of Ogbimi and Omu[3] amongst Nigerian women during normal pregnancy. However, Lafi *et al.*[20] reports an increased value of both IgG and IgM levels in pregnant Egyptian women with an enhanced IgG placental 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 malaria infection; 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[21,22]. Reports indicate that malaria infection is associated with CD4+ cell activation and up-regulation of pro-inflammatory cytokines[23]; both important for effective response of B-lymphocytes (responsible for immunoglobulin production) and cytotoxic T-lymphocytes (CD8+)[24]. 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 effect or cells[6,25]. 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[10]. This finding is not consistent with the report of Akinpelu *et. al.*[10] 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 of HIV induced immune suppression when the study was conducted[26]. 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[26]. Although, the suppression of maternal immune sensitivity during pregnancy is to prevent fetal allograft rejection[20] studies have revealed a further though partial impairment of humoral immune response to malaria in HIV-infected pregnant women[7,27]. HIV infection induced impairment of malarial immunity is greatest in the most immune suppressed women and could explain the increased susceptibility to malaria seen in pregnant women with HIV infection[27].

## 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 malaria in pregnancy IgG and IgM levels were consistently and significantly low and amongst HIV sero-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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