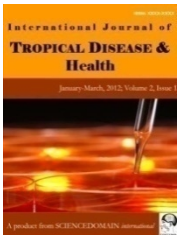

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# Seroprevalence of Herpes Simplex Virus Infections among Pregnant Women Attending Antenatal Clinic in Benin, Nigeria

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***Author's contribution***

*This whole work was carried out by the author KEI.*

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## ABSTRACT

**Aims:** In many countries, genital herpes, which is predominantly caused by HSV-2 in Nigeria, has become a public health problem of such increasing magnitude that national genital herpes control programmes have been instituted.. Advocacy for formulation of such a programme and the types of interventions to be included in the programme in Nigeria will require data on the prevalence of the disease and the associated factors. Moreover, most of the candidate vaccines against HSV-2 tend to fail when administered to HSV-1 infected persons. The utility of such vaccines in Nigeria will depend on the current seroprevalence of HSV-1 infections.
The aim of this study is to assess the seroprevalence of HSV-1 and HSV-2 infections among pregnant women attending antenatal clinic in University of Benin Teaching Hospital (UBTH); and to verify the association between HSV-2 infection and HIV-status, age, parity, level of education and positive history of painful genital ulcers.
**Study Design:** Cross-sectional study.
**Place and duration of the study:** 264 pregnant women attending antenatal clinic in UBTH were prospectively and consecutively included in the study which took place between December, 2011 and August, 2012.
**Methodology:** The patients were tested for HSV-1 IgG and IgM; and for HSV-2 IgG and IgM, using gG type-specific ELISA technique. Their HIV statuses were also determined. Data analysis was done using SPSS version 16.
**Results:** HSV-2 antibodies were present in 44.3% while HSV-1 antibodies were present

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96.6% of the participants. Age, HIV-status and marital status were found to be significantly associated with occurrence of HSV-2 antibodies; while parity, level of education and history of painful genital ulcers had no significant association.
**Conclusion:** Seroprevalence of HSV-1 infection was 96.6% while that of HSV-2 infection was 44.3%. Factors that were significantly associated with occurrence of HSV-2 infection included age, marital status and HIV status.

*Keywords: HSV-1; HSV-2; Seroprevalence; serostatus.*

## 1. INTRODUCTION

Genital herpes is a disease caused by Herpes Simplex Viruses, which belong to the alphaherpesvirinae subfamily. In Nigeria, as in most sub-Saharan African countries, this disease is predominantly caused by Herpes Simplex Virus type 2 (HSV-2) and has become a public health problem of such an increasing magnitude that a national genital herpes prevention programme has become urgently needed for its control [1,2,3]. It affects an estimate of 356 million (about 16%) persons in the reproductive age range, worldwide [1]. The disease has been described as an insidious and progressive worldwide pandemic; and different countries are said to be have different grades of the epidemic [1]. The epidemiological factors determining the persistent spread of this disease are similar to those of Human Immunodeficiency Virus (HIV) infection; and both diseases have become mutually reinforcing epidemics [4,5]. Among countries in the sub-Saharan region, in which resides the vast majority of people living HIV/AIDS, the prevalence of genital herpes in females of the reproductive age group has been said to range between 30%-80% [6]. This highlights the fact that control of HIV and all other sexually transmitted infections (STIs) ought to be comprehensive and not focused on any particular agent.

The occurrence of genital herpes among pregnant women, though clinically inapparent in most of the cases, is particularly associated with several problems in the woman and in the offspring [7]. The most devastating direct impact of maternal genital herpes is the neonatal disease [1,7]. Genital herpes in pregnancy is associated with definite risks of meningoencephalitis and disseminated herpes in the neonate [1,8]. Neonatal meningoencephalitis kills about 50% of affected babies and leaves the survivors with permanent neurologic deficit [7,8]**;** while disseminated neonatal disease kills close to 90% of the infected [9,10]. Moreover, congenital anomalies in the newborn can result [11,12]. The risk of transmission of this infection from mother to newborn can increase 10-fold if the primary/initial maternal infection is acquired during near term [13]. This risk of transmission and the severity of the neonatal disease has been reported to increase further if the woman is HIV-infected [14]; and moreso, if the newly infected pregnant woman did not have prior HSV-1 infection [1,14].

Primary HSV infection in pregnancy is also associated with obstetric complications like intrauterine growth retardation, intrauterine death, prematurity and spontaneous abortion [6,7,15,16]. In the clinically apparent maternal primary genital herpes, painful genital ulceration is the commonest presenting feature [17]. In some cases of primary herpes, however, on the disease can potentially lead to a fatal disseminated herpes in the pregnant woman, especially in immunocompromised states [17]. In addition to the pains due to maternal genital ulcer disease, the psychosocial impact of the disease on family life is enormous [18]. Genital herpes also leads to enhanced transmission of HIV infection,

including enhanced maternal-to-fetal HIV transmission [1,18]. Furthermore, every HSV infection is lifelong, despite adequate therapy, and the host is subsequently ever at risk of severe disease, should there be immunodeficiency [17].

It is therefore imperative that definite policy-based control measures need to be put in place to prevent the occurrence of primary infection during pregnancy; and to effectively manage those who are infected, with a view to preventing the occurrence of associated complications [2]. Advocacy for formulation of such policy guidelines and the design of the specific interventions require local data on the prevalence of the disease and the associated factors. As the disease is not often detectable clinically, there is recourse to serology for retrospective detection and prevalence studies. Herpes Simplex Virus type 2 (HSV-2) seroprevalence studies provide reliable approximations of genital herpes prevalence in all regions [1].There's yet no published data on the prevalence in the Nigerian general population, though are prevalence values among commercial sex workers and among sexually transmitted infection clinic attendees [19,20]. In the absence of general population-based studies, data based on antenatal clinic attendees, as in this study, can be taken as significantly representative of the general population data [1].

So much effort is being made to develop vaccines against HSV-2 and many of the candidate vaccines are ineffective on HSV-1 seropositive persons [4]. The proportion of HSV-1 seronegative persons in Nigeria, as derived from this study, will determine the possible usefulness of the vaccine here. A study done in the 1970's in Nigeria found the HSV-1 prevalence among youths and adults to be 100% [21]. However, recent reports show that adult HSV-1 prevalence values decline as socioeconomic status and environmental hygiene improve [22]. Therefore, data on the current seroprevalence of HSV-1 infections, as well as HSV-2 infections, should be vital to policy planning in Nigeria especially if vaccine-based intervention is in view.

## 2. MATERIALS AND METHODS

### 2.1 Study Area, Population and Design

Study location was University of Benin Teaching Hospital (UBTH), located in Benin, Edo state capital city of Nigeria. UBTH is a tertiary health care centre that serves as a referral centre in Southern Nigeria. Cross-sectional study design was adopted. Two hundred and sixty-four (264) ante-natal clinic attendees of UBTH were consecutively and prospectively recruited in a study that took place between December, 2011 and August 2012.

Data sources were structured interviewer-administered questionnaire, patients case notes and laboratory investigations. The questionnaire was used to elicit sociodemographic and obstetric information; along with information on the occurrence of genital ulcers. Patients' sera were used for HSV-1 IgG, HSV-1 IgM, HSV-2 IgG, HSV-2 IgM, and HIV immunoassays.

### 2.2 Laboratory Procedures

Blood samples were collected in 5 ml plain vacutainer tubes and allowed to clot and sera separated by centrifugation at room temperature. Storage was in cryovials at $-20^0$C.

#### 2.2.1 HSV-1 and HSV-2 IgG assay procedure

This utilized Enzyme Linked Immunosorbent Assay (ELISA) kit by Dia. Pro. Diagnostic Bioprobes Milano – Italy. This is a glycoprotein G-based enzyme-linked immunosorbent assay (ELISA) technique and test result was qualitative.

All specimens and kit reagents were brought to room temperature and gently mixed. The laboratory procedures were performed according to the manufacturer's instructions [23].

#### 2.2.2 HSV-1 and HSV-2 IgM assay procedure

The kit used was Dia. Pro. Diagnostic Bioprobes Milano – Italy**;** and the assays were performed in accordance with manufacture's instructions [24].

#### 2.2.3 HIV immunoassay procedure

The HIV statuses of the respondents were previously determined using Determine ® HIV ½ by Inverness Medical Innovations South Africa; and HIV 1 & 2 STAT PAK Assay kit by CHEMBIO Diagnostic system, INC, New York, USA.

Each batch of tests ran with both positive and negative controls and results were qualitative.

### 2.3 Data Analysis

Data collected was analyzed using the SPSS version 16 computer software. Fishers exact was used to test associations. Statistical significance was ascribed based on P values < 0.05.

## 3. RESULTS

The ages of the 264 included antenatal clinic attendees ranged from 18 years to 44 years. Their mean age was 30.6 ± 5.1 years. While majority (70.5%) of the sample population were between 26 and 35 years of age, age groups 15-20 and 41-50 were in the minority (represented by 1.1% and 2.3% of the respondents). The 46 -50 years age group was not represented.

Most (85.3%) of the participants were married.

Ninety-three percent (93.6%) of the participants completed secondary education, as 75% of them were educated above secondary level and 18.6% stopped at secondary level of education. (Table 1)

**Table 1. General characteristics of respondents**

| Characteristics | Frequency | Percent (%) |
|---|---|---|
| **Age Group (Years)** | | |
| 15-20 | 3 | 1.1 |
| 21-25 | 36 | 13.6 |
| 26-30 | 96 | 36.4 |
| 31-35 | 90 | 34.1 |
| 36-40 | 33 | 12.5 |
| 41-45 | 6 | 2.3 |
| **Marital Statuses** | | |
| Married | 225 | 85.3 |
| Single | 21 | 7.9 |
| Divorced | 9 | 3.4 |
| Widowed | 9 | 3.4 |
| **Levels Of Education** | | |
| Graduate and above | 81 | 30.7 |
| Post-secondary | 117 | 44.3 |
| Secondary completed | 49 | 18.6 |
| Secondary uncompleted | 5 | 1.9 |
| Primary completed | 10 | 3.8 |
| Primary uncompleted | 2 | 0.8 |
| **Hiv Status** | | |
| Positive | 32 | 12.1 |
| Negative | 232 | 87.9 |

Most of the participants were recruited either in their second (39.8%) or in their third (45.5%) trimesters of pregnancy; while 14.7% were seen in their first trimesters (Table 2).

Majority (43.6%) of the respondents were nulliparae. Twenty-eight percent (28%) of them were primiparae; 27.6% were multi-parae, while only two (0.8%) of them were grand-multiparae. (Table 2)

**Table 2. Obstetric characteristics of respondents**

| Characteristics | Frequency | Percent |
|---|---|---|
| **Gestational Ages** | | |
| $1^{ST}$ Trimester | 39 | 14.7 |
| $2^{ND}$ Trimester | 105 | 39.8 |
| $3^{RD}$ Trimester | 120 | 45.5 |
| **Parity** | | |
| Nullipara | 115 | 43.6 |
| Primipara | 74 | 28.0 |
| Para-2 | 49 | 18.6 |
| Para-3 | 16 | 6.0 |
| Para-4 | 8 | 3.0 |
| Para-5 or more | 2 | 0.8 |

HSV-2 antibodies were present in 117 of the 264 respondents, giving an HSV-2 seroprevalence of 44.3%. HSV-1 antibodies were present in 255 of the 264 respondents,

giving an HSV-1-seroprevalence of 96.6%. All the HSV-1 antibodies were of IgG biotype (Table 3)

**Table 3. Prevalence of HSV-1 antibody biotypes**

| HSV type (antibody biotype/s) | Number of antibody biotype/s present | Percent | Number tested |
|---|---|---|---|
| HSV-1 IgG only | 255 | 96.6% | 264 |
| HSV-1 IgG +igM | 0 | 0% | 264 |
| HSV-1 IgM only | 0 | 0% | 264 |

Most (110) of the 117 HSV-2 sero-positive participants had IgG biotype only; 3 participants had both IgG and IgM biotypes; while 4 had only IgM biotypes. A total of 7 participants (2.7%) had IgM biotypes (Table 4).

**Table 4. Prevalence of HSV-2 antibody biotypes**

| HSV type (antibody biotype/s) | Number of antibody biotype/s present | Percent | Number tested |
|---|---|---|---|
| HSV-2 IgG only | 110 | 41.7 | 264 |
| HSV-2 IgG + IgM | 3 | 1.1 | 264 |
| HSV-2 IgM only | 4 | 1.5 | 264 |

The prevalence of HSV-2 antibodies was significantly higher among respondents of higher age groups than among those of lower age groups.

The prevalence of HSV -2 antibodies was generally lower among participants who were educated beyond secondary level than among those who were less educated. However, the difference was not significant. ($p = .145$).

There was statistically significant difference between the prevalence of HSV-2 infection among the married respondents and the various unmarried counterparts. ($p = .031$)

Parity was not found to be significantly associated with the occurrence of HSV-2 antibodies. ($p= .144$) (Table 5).

The prevalence of HSV-2 antibodies among the HIV-infected was significantly higher than that of the HIV-uninfected. ($p = .022$).

Only 9.5% of the participants recalled having had genital ulcers. The prevalence of HSV-2 antibodies was higher among those with negative history of painful genital ulcers than among those with positive history. There was no significant association of history of painful genital ulcers with occurrence of HSV-2 antibodies (Table 5).

**Table 5. HSV-2 serostatus and participant characteristics**

| Characteristics | HSV-2 antibody positive (%) | No. tested (%) | P-value |
|---|---|---|---|
| **Age groups** | | | |
| 15-20 | 2 (66.7) | 3 (1.1) | .04 |
| 21-25 | 11(30.6) | 36 (13.6) | |
| 26-30 | 36 (37.5) | 96 (36.4) | |
| 31-35 | 42 (46.7) | 90 (34.1) | |
| 36-40 | 23 (69.7) | 33 (12.5) | |
| 41-45 | 3 (50) | 6 (2.3) | |
| **Level of education** | | | |
| Graduate and above | 33 (40.7) | 81(30.7) | .145 |
| Post-secondary | 50 (42.7) | 117 (44.3) | |
| Secondary completed | 23 (46) | 50 (18.9) | |
| Secondary uncompleted | 5 (100) | 5 (1.9) | |
| Primary completed | 6 (60) | 10 (3.8) | |
| Primary uncompleted | 0 (0) | 1 (0.4) | |
| **Marital status** | | | |
| Married | 94 (41.8) | 225 (85.3) | .031 |
| Single | 10 (47.6) | 21 (7.9) | |
| Divorced | 7 (77.8) | 9 (3.4) | |
| Widowed | 6 (66.7) | 9 (3.4) | |
| **Parity** | | | |
| Nullipara | 42(36.5) | 115 (43.6) | .144 |
| Primipara | 37(50) | 74 (28.0) | |
| PARA-2 | 22 (44.9) | 49 (18.6) | |
| PARA-3 | 10 (62.5) | 16 (6.0) | |
| PARA-4 | 6 (75.0) | 8 (3.0) | |
| PARA-5 OR MORE | 0(0.0) | 2 (0.8) | |
| **HIV status** | | | |
| Positive | 21(65.6) | 32 (12.1) | .022 |
| Negative | 96 (41.4) | 232 (87.9) | |
| **History of painful genital ulcers** | | | |
| Positive | 9 (36) | 25 (9.5) | .399 |
| Negative | 108 (45.2) | 239 (90.5) | |

Only 9 of the participants (3.4%) were HSV-1 negative. HSV-1 antibodies were 100% prevalent among the younger age groups (Table 6).

**Table 6. Presence of hsv-1 antibodies among the various age groups**

| Age groups (years) | Presence of HSV-1 antibodies | |
|---|---|---|
| | Positive (%) | No. tested (%) |
| 15-20 | 3(100) | 3(1.1) |
| 21-25 | 36(100) | 36(13.6) |
| 26-30 | 93(96.9) | 96(36.4) |
| 31-35 | 87(96.7) | 90(34.1) |
| 36-40 | 30(90.9) | 33(12.5) |
| 41-45 | 6(100) | 6(2.3) |
| **Total** | 255 | 264 |

## 4. DISCUSSION

In this study, the seroprevalence of HSV-2 infection was found to be 44.3%. In accordance with the observation that seroprevalence values among pregnant sub-populations correlates consistently with those of the general population, the result of this study can be presumed to approximate seroprevalence of HSV-2 infection in Nigeria [1]. This prevalence value is high and no other published report on the seroprevalence of HSV-2 infection among the pregnant population in Nigeria was found. Lower HSV-2 seroprevalence findings of 20.7%, and 26% were, however, found among pregnant women in Tanzania and Senegal, all of sub-Saharan Africa region [25,26]. When compared to other settings, the value in this study is much higher than the HSV-2 seroprevalences of 7.5% and 21% reported among pregnant women in India and USA respectively [27,28].

The mutual re-inforcement of transmission efficiency exhibited by HIV-infection and HSV-2 infection could be contributory to this high HSV-2 prevalence in Nigeria. Moreover, the infection was significantly more prevalent among the HIV-infected participants than among the HIV-uninfected counterparts, in this study. Detailed study of the epidemiology of HSV-2 infection in the Nigerian locality is necessary to enable accurate definition of strategies, targets and possible mode of integration of genital herpes and HIV-infection control programmes. The myriad of potential, and largely unexplored, problems associated with high prevalence of genital herpes in Nigeria demands that the Nigerian Federal Ministry of Health exercise greater proactivity in the her response to this infection [1,2]. The response should involve ascertainment of the burden, risk factors, and deterrent of the infection using wider multi-centred population survey. The national survey, with the appropriate sampling method for population studies, will overcome the limitations of this study. Thus, this study could be seen as a pilot; and the nationwide population survey should follow soon, so as to generate reliable data-base for integration of HSV-2 control into existing HIV control programmes. The challenges being faced in the control of HIV infection may be strongly related to the silent but very active genital herpes pandemic. It is well known that effective control of sexually transmitted diseases ought to be comprehensive, rather than focused on a solitary disease agent.Therefore national response to the HIV scourge may not be adequate until there is an appropriate specific response to HSV-2 infection. Due to the perculiar problems associated with genital herpes in pregnancy, pregnant women must be included, among other control targets. Such programmes should involve several interventions ranging from specific health education to testing of target populations. Consequent on limited resources, testing all

pregnant women for HSV-2 infection may not be feasible. In this study, significant associations between HSV-2 infections and marital status, age and HIV-status were found. These three associated characteristics could form the basis of the selection of pregnant women for screening tests. Specific interventions could be designed for the tested pregnant women based on their sero-status. For instance HSV-2 sero-negative women could benefit from sexual health education; while HSV-2 IgM seropositive ones could benefit from close monitoring of the pregnancy, especially, during the peurperium, when the chance of maternal-to-child transmission is high. Such primary infections occurring during pregnancy (especially late pregnancy) may require elective caesarean section and/or presumptive treatment of the neonate for neonatal herpes [29,30]. In this study, 2.7% of the study population had IgM biotype of HSV-2 antibodies, indicating that HSV-2 transmission is on-going in Nigerian communities [31]. The outcome of these pregnancies that are asscociated with IgM HSV-2 antibodies in this environment require ascertaining.

In this study, there was no significant association between HSV-2 seroprevalence and positive history of genital ulcers. The significance of this finding may be hampered by the non-specific nature of the pathogenesis of genital ulcers. Ulcers in the genital area could be caused by microbes other than HSV. These include other sexually transmitted infections like granuoma inguinale, syphilis, soft chancre, lymphogranuloma inguinale; non-sexually transmitted infections like herpes zoster, furuncles, scabies, pediculosis, erythema multiforme, and trauma. Moreover, only a minority of the participants could recall having had painful genital ulcers, which points to the reduced importance of this factor in the Nigerian environment.

The seroporevalence of HSV-1, in this study, was found to be 96.6%. This value is only 3.4% lower than that the 100% seroprevalence found in a study done in Western Nigeria about 40 years ago [21]. Less HSV-1 seroprevalence value of 57.7% was reported from USA; and a reduction of 6.9% occurred between 1999 and 2004 [32]. These reduction was attributed to improvement in personal and environmental hygiene [32]. The less significant reduction in HSV-1 seroprevalence in Nigeria may be due to the inconsistent environmental sanitation improvements; as our urban areas are rapidly turning to slums.

The HSV-1 seroprevalence result in this study conforms to the finding that HSV-1 seroprevalence still tends to be high as from age five and above, in sub-Saharan African countries; and this is due to early acquisition of the infection in childhood by non-sexual means [2]. Consequent on this, HSV-1 seroprevalence among adolescents and young adults in these countries tend to be more than 90%; and this has been observed in Eritrea, Uganda, and Central African Republic [33]. The implications of this high HSV-1 seroprevalence are that the rate of childhood HSV-1 infection is still very high in our communities. The early acquisition of HSV-1 infection is attested to by the fact all those in the younger age groups had the infection; and all the HSV-1 infected participants had IgG biotype. The protective effect of HSV-1 antibodies implies that the incidence of HSV-1 genital herpes will remain negligible [2].

The high prevalence of HSV-2 infection in the presence of near 100% HSV-1 seroprevalence confirms that the protective effect of HSV-1 antibodies on HSV-2 infection is not complete. The extent of HSV-1-mediated protection of the Nigerian population (especially the pregnant) from the various complications of HSV-2 infection also requires ascertaining.

Since there is a minority (3.4%) of the population that are HSV-1 seronegative, this sub-population of pregnant women and their unborn babies may require specific protection from primary HSV-2 infection and the several severe obstetric complications.

If the fight against HIV must be won, HSV-2 infection must be controlled. HSV-2 vaccine development efforts should therefore be sustained. Many of the candidate HSV-2 vaccines have been found to be rendered ineffective by HSV-1 antibodies [34]. It seems instructive, from the findings of this study that HSV-2 vaccine candidates should be designed specifically for sub-Saharan Africa where the HSV-1 seroprevalence is high.

## 4. CONCLUSIONS

The seroprevalence of HSV-2 infections among pregnant women attending antenatal clinic in UBTH was found to be 44.3%. The factors that were found to be significantly associated with occurrence of HSV-2 infection were age, marital status and HIV-status. HSV-1 seroprevalence was found to be 96.6%.

## CONSENT

Informed written consent was obtained from each of the included patients for publication of this work.

## ETHICAL CONSIDERATIONS

Approval was sought and obtained from the Health Research Ethics Committee of University of Benin Teaching Hospital for this research work.

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## COMPETING INTERESTS

This was a self-sponsored project. No competing interests exist.

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