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Obstetric outcomes of human Herpes virus-2 infection among pregnant women in Benin, Nigeria

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Abstract

Objective: This study investigated the obstetric outcomes of herpes simplex virus (HSV-2) infection among pregnant women.

Materials and Methods: In this prospective cohort study, a total of 674 consenting pregnant women attending ante-natal clinic in the University of Benin Teaching Hospital and Central Hospital Benin were recruited between November 2011 and December, 2012. The women were screened for HSV-1, and HSV-2 using glycoprotein-G-based type-specific Enzyme Linked Immunosorbent Assay on archived blood samples; and were followed up to the delivery period and postnatal clinic. The HSV-2-seronegative participants underwent second blood sampling for HSV-2 IgG and IgM assay during the delivery period. The patients were thus categorized into "HSV-2 seropositive", "HSV-2–seronegative," and "incident HSV-2 infection" cohorts. The pregnancy outcomes were assessed by review of hospital records. Data analysis was with SPSS version 16 software.

Results: Of 674 pregnant women surveyed, 312 (46.3%) were HSV-2 seropositive; while 362 (56.7%) were HSV-2 seronegative. Comparing the "HSV-2 seropositive" and "HSV-seronegative" groups, there were no significant differences in occurrence of low birth weight (LBW), prematurity, spontaneous abortions, and stillbirth events (P = 0.96; 0.95; 1.0; and 0.77, respectively). Comparing the "incident HSV-2 infection" with the "HSV-2 seronegative" groups, the relative risks of occurrence of LBW deliveries, preterm deliveries, and stillbirths were 12.6, 25.1, and 4.5, respectively.

Conclusion: First episode HSV-2 infection among pregnant women in Benin, Nigeria is associated with an increased risk of occurrence of spontaneous abortion, LBW delivery, stillbirths, and preterm delivery.

Key words: Benin, herpes simplex virus-2, obstetrics outcomes, pregnant women, seroprevalence

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Introduction

Human herpes simplex virus 2 (HSV-2) infections presents in two clinical forms: First episode or recurrent.[1] First episode HSV-2 infections may be primary or nonprimary, depending on the absence or presence of preexisting heterologous antibodies, respectively.[2-4] HSV-2 infection in pregnancy is reported to be associated with increased frequency of occurrence of certain negative obstetric outcomes: Spontaneous abortions, intrauterine fetal death (IUFD), stillbirths, preterm labor, fetal malformations, congenital herpes, neonatal herpes, intrauterine growth retardation, intrauterine death, low birth weight (LBW) deliveries, and spontaneous abortions.[5-7] These obstetric complications and other complications of HSV-2 infection, have been reported to be mitigated by the presence of heterologous antibodies, which was reported to be 100% prevalent in Ibadan, Nigeria in a study done about 35 years ago.[1,8] It is necessary to assess the pattern of occurrence

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of these complications among pregnant women. This information will further enable a clearer understanding of the burden of HSV-2 infection in Nigeria. Such data will create more evidence-base for design of interventions.

The study was therefore aimed at assessing the effect of HSV-2 infection on the obstetric outcomes among pregnant women in Benin, Nigeria.

Materials and Methods

Study area and design

The participants were consenting pregnant women registered in the Obstetrics and Gynecology Departments of University of Benin Teaching Hospital and Central Hospital, Benin, the two major hospitals serving the Benin metropolis, other parts of Edo state and neighboring states. Participants in this cohort study were enrolled between November 2011 and December 2012.

Ethical considerations

Ethical approval was obtained from Health Research Ethics Committee of University of Benin Teaching Hospital. Consent was obtained from the Obstetrics and Gynaecology departments for accessing patients' data. Informed consent was obtained from the participants for this research. All baseline HSV-2-seronegative participants were educated on the need to prevent acquisition of HSV-2 infection during the pregnancy. For those who acquired HSV-2 infection during the follow-up period, they and their obstetricians were informed, and suppressive acyclovir therapy was recommended for 2 weeks prior to expected delivery date.

Sampling and data collection

Baseline data

The consenting participants were recruited prospectively as they booked at the ante-natal clinic registration centers. The nonconsenting and those who booked at >28 weeks gestational age were excluded. Baseline data on sociodemographic and obstetric history were obtained using structured self-administered questionnaire and patient's case notes. Archived blood samples were obtained to assay HSV-2 and HSV-1 IgG antibodies using glycoprotein-G-based (type-specific) Enzyme-Linked Immunosorbent Assay (ELISA).

Follow-up data

All the baseline study participants (both HSV-2 seropositive and HSV-2 seronegative) were followed up to delivery. Data on gestational age, birth weight, and baby's condition were obtained from delivery notes. In addition to hospital obstetric records, the pregnancy outcomes were also assessed using personal communication. All the participants who were at risk of incident HSV-2 infection (those who were HSV-2 seronegative at baseline), in addition to being followed up to delivery, underwent a second blood sampling for HSV-2 antibody (IgM and IgG) assay around delivery time. Participants with LBW and prematurity complications were followed up to the postnatal clinics to assess infant survival. An HSV-2 seronegative participant whose pregnancy outcome was known, including those who had stillbirths and spontaneous abortion, but who did not undergo second blood sample collection was excluded in the follow-up data analysis.

Research assistants (laboratory technicians attached to the ante-natal clinic laboratories; nurses/midwives attached to the ante-natal clinics, the labor room, and the family planning units) were trained on the baseline and follow-up protocols. Adequate telephone contact was maintained with the participants to obtain feedback on the progress of their pregnancies, to encourage compliance with clinic appointments and to ensure that they did not deliver at home.

Laboratory procedures

Blood samples were collected in 5 ml plain vacutainer tubes and allowed to clot, and sera were separated by centrifugation at room temperature. Storage was in cryovials at −20°C.

Herpes simplex virus-1 and HSV-2 IgG assay procedure

An Enzyme-Linked Immunosorbent Assay kit by Dia. Pro. Diagnostic Bioprobes Milano – Italy was used. This is a glycoprotein-G-based ELISA technique and test result was qualitative.[9,10] The laboratory procedures were performed according to the manufacturer's instructions, and quality control was built into the test protocols.[10,11]

Herpes simplex virus-2 IgM assay procedure

The kit used was Dia. Pro. Diagnostic Bioprobes Milano – Italy; and the assays were performed in accordance with manufacturer's instructions. Each batch of tests ran with both positive and negative controls, and results were qualitative.[12]

Definitions

Herpes simplex virus-seropositivity and HSV-seronegativity were defined as presence or absence of type-specific antibodies.

First trimester was defined as the period from conception to 12 completed weeks of gestation; second trimester as the period from the beginning of week 13 through week 28; while third trimester was defined as the period from the beginning of week 29 to the onset of labor.

Complicated pregnancy was defined as any pregnancy which became associated with any of the following negative outcomes/events: Spontaneous abortions, IUFD, LBW, prematurity, stillbirths, neonatal herpes, and congenital malformations.

Spontaneous abortion was defined as a loss of pregnancy before 20 weeks gestational age.

Preterm labor was defined as labor occurring after 20 weeks and before 37 weeks from the 1st day of the woman's last menstrual period.

Low birth weight infant was defined as birth weight <2500 g.

Physical observation was used to assess the newborns for complications. As neonatal herpes is almost always symptomatic, neonatal herpes complication was assumed to be ruled out if there were no typical mucocutaneous lesions, and the baby is adjudged clinically healthy.

Stillbirth was defined as a delivery of a dead fetus after 28th week of pregnancy.

Frequency of occurrence of obstetric complications was defined as the ratio of the number of occurrences to the number of participants at risk.

Seroconversion frequency was defined as the percent proportion of seroconversions relative to those at risk during the follow-up period.[2]

Herpes simplex virus-2 seroconversion was defined as the detection of IgG and/or IgM antibodies in any previously HSV-2-seronegative participant using the glycoprotein-G-based type-specific ELISA assay.

Data analysis

Follow-up participants were categorized into "HSV-2 seropositive" (those who were seropositive at baseline), "HSV-2 seronegative" (those who were seronegative at baseline and did not seroconvert during the follow-up period), and "incident HSV-2 infection" groups (those who were seronegative at baseline but seroconverted during follow-up).

The relative frequency of specific outcomes, namely the occurrence of spontaneous abortions, stillbirths, preterm labor, LBW delivery, IUFD, neonatal herpes, and congenital malformations was compared among the three categories of follow-up participants.

Chi-square and Fisher's exact test were used to compare the frequencies. Risk ratio calculations (and the 95% confidence intervals [CIs]) were done to assess the risk of occurrence of the complications among the "incident HSV-2 infection" participants, relative to "HSV-seronegative" participants.

SPSS version 16 (SPSS Inc, Chicago, USA) was used for statistical analysis; and statistical significance was assessed based on $P < 0.05$.

Results

General and obstetric characteristics of baseline study participants

A total of 674 participants were enrolled in the baseline study. The ages of these participants were between 18 and 44 years (mean = 30.6 ± 5.2 years). Most (85.2%) of the participants were married. They were either Christians or Muslims, in the ratio 4.7:1. Most of the members of the

Table 1: Participants' general characteristics and their HSV-2 statuses

Characteristics	No HSV-2 seropositive (%) (*n*=312)	Total no tested (%) (*n*=674 (100))
Age group (years)		
16-20	2 (0.6)	7 (1)
21-25	38 (12.2)	98 (14.5)
26-30	96 (30.8)	242 (35.9)
31-35	109 (34.9)	225 (33.4)
36-40	59 (18.9)	86 (12.8)
41-45	8 (2.6)	16 (2.4)
Religion		
Christianity	250 (80.1)	556 (82.5)
Islam	62 (19.9)	118 (17.5)
Marital status		
Married	245 (78.5)	574 (85.2)
Single	33 (10.6)	53 (7.8)
Divorced	17 (5.4)	22 (3.3)
Widowed	17 (5.4)	25 (3.7)
Level of education		
Graduate and postgraduate	93 (29.8)	210 (31.2)
Postsecondary	129 (41.3)	292 (43.3)
Secondary completed	60 (12.2)	128 (19.0)
Secondary uncompleted	14 (4.5)	14 (2.1)
Primary completed	16 (5.1)	27 (4.0)
Primary uncompleted	0 (0)	3 (0.4)

HSV=Herpes simplex virus

Table 2: Obstetrics characteristics and HSV-2 statuses of all participants

Characteristics	No HSV-2 seropositive (%) (*n*=312)	Total no tested (%) (*n*=674 (100))
Initial gestational age		
1st trimester	28 (9.0)	99 (14.7)
2nd trimester	136 (43.6)	268 (39.8)
3rd trimester	138 (44.2)	307 (45.5)
Parity		
Nullipara	116 (37.2)	293 (43.5)
Primipara	92 (29.5)	190 (28.2)
Para-2	61 (19.6)	123 (18.2)
Para-3	27 (8.7)	43 (6.4)
Para-4	16 (5.1)	20 (3.0)
Para-5 or more	0 (0)	5 (0.7)

HSV=Herpes simplex virus

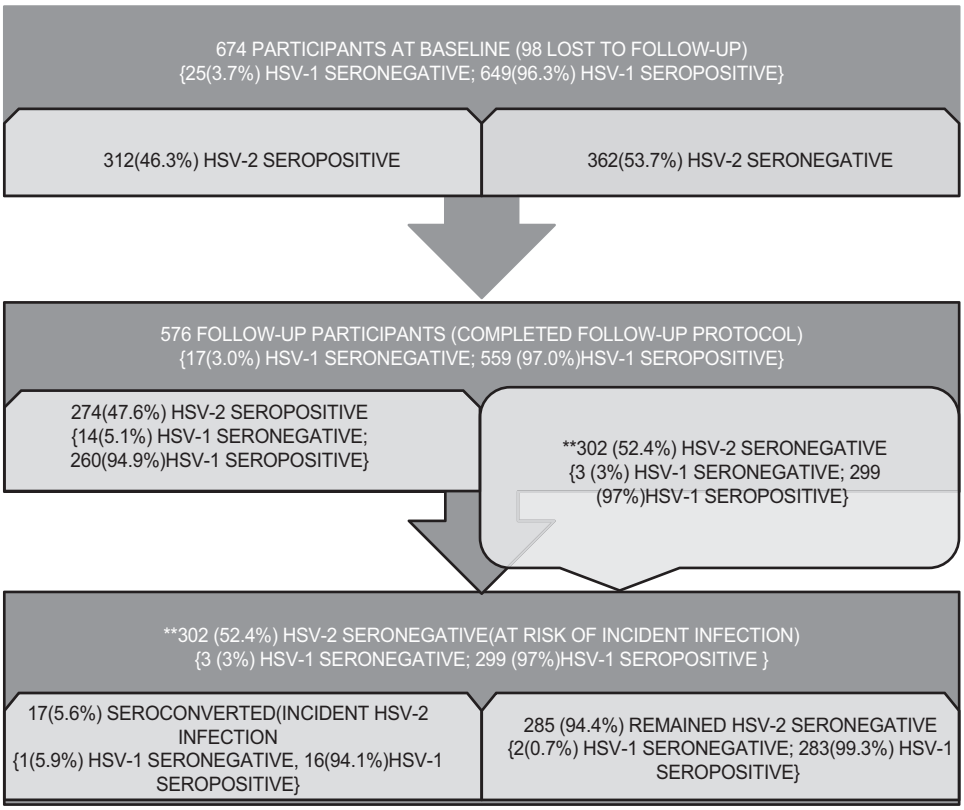

Figure 1: Flow diagram illustrating the herpes simplex virus (HSV-1) and HSV-2 serological profile of the participants

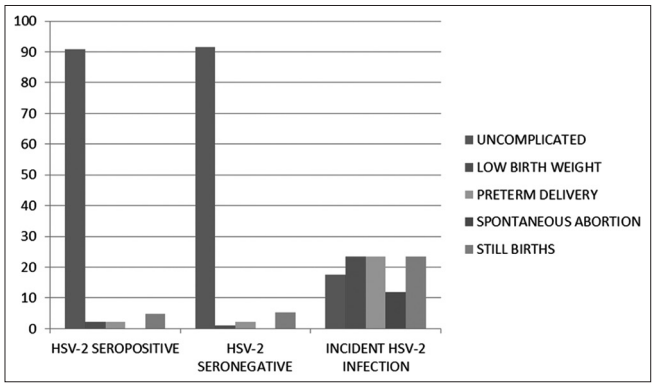

Figure 2: General pattern (percent frequencies) of occurrence of complications in the three cohorts

baseline study population had good education. Only 6.5% did not achieve complete secondary education [Table 1].

Majority (85.3%) of the participants were recruited either in their second or their third trimesters of pregnancy; while 14.7% were first seen in their first trimesters. Also most (43.5%) were nulliparae. Twenty-eight percent (28.2%) of them were primiparae; while a total of 27.6% of them were multi-parae. Only 2 (0.7%) of the participants were grand multiparae [Table 2].

Herpes simplex virus statuses of all participants

Three hundred and twelve (46.3%) of the participants were HSV-2 seropositive; while 362 (56.7%) were HSV-2 seronegative and were at risk of the first episode (primary or nonprimary) HSV-2 infection. Prevalence of HSV-1 antibodies among the participants was 96.3% (649/674).

Follow-up data

Characteristics of follow-up participants

Only 576 of the 674 baseline study participants completed the follow-up protocols, giving a response proportion of 88.4%. This proportion consisted of 274 HSV-2 seropositive and 302 HSV-2 seronegative individuals. Seventeen (5.6%) of the 302 HSV-2 seronegative women seroconverted while 285 remained seronegative throughout the follow-up period. The 576 participants were therefore categorized into three: 274 "HSV-2 seropositive," 285 "HSV-2 seronegative," and 17 "incident HSV-2 infection" cohorts [Figure 1].

The reason for incomplete follow-up among the 11.6% (98/674) participants who were lost to follow-up included: Refusal to be venepunctured the second time; residence relocation; changing ante-natal clinic to nearby health care centers; loss of pregnancy by baseline HSV-2 seronegative participants with consequent withdrawal of participation; and unclear documentation of archived blood samples. Some gave no reason (they just stopped communicating).

Table 3: Relative frequencies of obstetrics complications among the three cohorts of follow-up participants

Outcome of pregnancy	Frequency of occurrence (%)			Total (%)
	HSV-2 seropositive (*n*=274)	HSV-2 seronegative (*n*=285)	Incident HSV-2 infection (*n*=17)	
Uncomplicated	249 (90.9)	261 (91.5)	3 (17.6)	513 (89.1)
LBW	6 (2.2)	3 (1.0)	4 (23.5)	13 (2.3)
Spontaneous abortion	-	-	2 (11.8)	2 (0.3)
Preterm labor	6 (2.2)	6 (2.1)	4 (23.5)	16 (2.8)
Stillbirth	13 (4.7)	15 (5.3)	4 (23.5)	32 (5.6)
Total	274 (100.0)	285 (100.0)	17 (100.0)	576 (100.0)

LBW=Low birth weight; HSV=Herpes simplex virus

Table 4: Occurrence of LBW, stillbirth, and preterm deliveries: HSV-2 seropositive group versus HSV-2 seronegative group

	Frequency of pregnancy outcome (%)	Total	P
LBW			
HSV-2 positive	6 (2.2)	274	0.96
HSV-2 negative	3 (1.0)	285	
Preterm delivery			
HSV-2 positive	6 (2.2)	274	0.93
HSV-2 negative	6 (2.1)	285	
Still birth			
HSV-2 positive	13 (4.7)	274	0.77
HSV-2 negative	15 (5.3)	285	

LBW=Low birth weight; HSV=Herpes simplex virus

Table 5: Obstetrics characteristics of follow-up participants and HSV-2 seroincidence

Characteristics	Total number tested (%), *n*=302	Number of seroconverters (%), *n*=17	*P*
GA at recruitment			
1st trimester	59 (19.5)	8 (13.6)	0.001
2nd trimester	110 (36.4)	9 (8.2)	
3rd trimester	113 (44.0)	-	
Parity			
Nulliparae	149 (49.3)	10 (6.7)	0.061
Primiparae	82 (27.2)	2 (2.4)	
Para-2	53 (17.5)	1 (1.9)	
Para-3	18 (6.0)	3 (25.0)	
Para-4	2 (0.7)	-	
Grand-multiparae	4 (1.3)	-	

HSV=Herpes simplex virus; GA=Gestational age

The characteristics of those who completed follow-up protocol were essentially similar to those of the baseline study participants.

General pattern of pregnancy outcomes

Irrespective of the follow-up participant category, the pregnancies of an overall majority (89.1%) of them were generally uncomplicated. The only observed adverse events were spontaneous abortion, delivery of LBW babies, preterm delivery, and still births. Seven out of the 32 cases of stillbirth (21.9%) were macerated.

There were no recorded incidences of IUFD, congenital malformations and neonatal herpes [Table 3 and Figure 2].

When categorized into three cohorts, (namely "HSV-2 seropositive", "HSV-2 seronegative," and "incident HSV-2 infection" groups, complications occurred most in the group with incident HSV-2 infection [Table 3 and Figure 2].

Occurrence of complications

"HSV-2 seropositive" versus "HSV-2 seronegative" groups: Between the "HSV-2 seropositive" and the "HSV-2 seronegative" groups, differences in the frequencies of occurrence of LBW delivery, preterm delivery, spontaneous abortion, and stillbirth events were not statistically significant ($P = 0.96$; 0.95; 1.0; and 0.77, respectively).

All the observed cases of spontaneous abortion occurred among the incident HSV-2 infection group, with a frequency of 11.8% [Tables 3 and 4].

Incident herpes simplex virus-2 infection and outcome of pregnancy

Seventeen of the 302 participants who were HSV-2 seronegative at baseline seroconverted during the follow-up period. This gave a seroconversion frequency of 5.6%. All the seroconversions took place among those who were recruited either in the first or the second trimesters of their pregnancy. While seroconversion frequency was highest among the first-trimester enrollees, none of the third trimester enrollees seroconverted. There was a significant association between seroconversion frequency and gestational age at enrollment ($P = 0.001$) [Table 5].

The greatest number of seroconversions took place among the nulliparae, who constituted a majority (43.5%) of the study population. Seroconversion frequency (percent proportion) was highest among para-3 enrollees, who constituted only 6.4% of the study population [Table 2]. There was no significant association between parity and seroincidence ($P = 0.06$) [Table 5].

Table 6: Risk of occurrence of obstetrics complications in the "incident HSV-2 infection" cohort relative to the HSV-2 seronegative cohort

	Obstetrics complications				
HSV-2 status	**Yes (%)**	**No (%)**	**Total tested (%), *n*=302**	**RR**	**95% CI of RR**
LBW					
Incident HSV-2 infection	3 (17.6)	14 (82.4%)	17 (5.6)	12.6	9.8-16.4
HSV-2 negative	4 (1.4)	28 (98.6)	285 (94.4)		
Preterm delivery					
Incident HSV-2 Infection	6 (35.3)	11 (64.7)	17 (5.6)	25.1	23.9-26.3
HSV-2 Negative	4 (1.4)	285 (98.6)	285 (94.4)		
Spontaneous abortion					
Incident HSV-2 Infection	2 (11.8)	15 (88.2)	17 (5.6)	∞	∞
HSV-2 negative	-	285 (100.0)	285 (94.4)		
Still birth					
Incident HSV-2 Infection	4 (23.5)	13 (76.5)	17 (5.6)	4.5	3.5-5.5
HSV-2 Negative	15 (5.3)	270 (94.7)	285 (94.4)		

LBW=Low birth weight; HSV=Herpes simplex virus; RR=Relative risk; CI=Confidence interval

Table 7: presence of HSV-1 antibodies and occurrence of complications in the "incident HSV-2 infection" group

HSV-1 status	**Obstetric complications**			***P***
	Delivery of LBW babies			
	Yes (*n*=4) (%)	**No (*n*=13) (%)**	**Total tested (*n*=17) (%)**	
HSV-1 seropositive	4 (100.0)	12 (92.9)	16 (94.1)	1.0
HSV-1 seronegative	0 (0.0)	1 (7.1)	1 (5.9)	
	Occurrence of preterm delivery			
	Yes (*n*=4) (%)	**No (*n*=13) (%)**	**Total tested (*n*=17) (%)**	
HSV-1 seropositive	3 (83.3)	13 (100.0)	16 (94.1)	0.353
HSV-1 seronegative	1 (16.7)	0 (0.0)	1 (5.9)	
	Occurrence of spontaneous abortions			
	Yes (*n*=2) (%)	**No (n=15) (%)**	**Total tested (*n*=17) (%)**	
HSV-1 seropositive	2 (100.0)	14 (93.3)	16 (94.1)	1.0
HSV-1 seronegative	0 (0.0)	1 (6.7)	1 (5.9)	
	Stillbirths			
	Yes (*n*=4) (%)	**No (*n*=13) (%)**	**Total tested (*n*=17) (%)**	
HSV-1 seropositive	4 (100.0)	12 (92.3)	16 (94.1)	1.0
HSV-1 seronegative	0 (0.0)	1 (7.7)	1 (5.9)	

LBW=Low birth weight; HSV=Herpes simplex virus

Table 8: Effect of HSV-1 antibodies on pregnancy outcomes in the HSV-2 seropositive group

HSV-1 status	**Obstetric complications**			***P***
	Delivery of LBW babies			
	Yes (*n*=6) (%)	**No (*n*=268) (%)**	**Total tested (*n*=274) (%)**	
HSV-1 seropositive	5 (1.9)	255 (98.1)	260 (94.9)	0.27
HSV-1 seronegative	1 (7.1)	13 (92.9)	14 (5.1)	
	Occurrence of preterm delivery			
	Yes (*n*=6)	**No (*n*=268)**	**Total tested (*n*=274)**	
HSV-1 seropositive	4 (1.5)	256 (98.5)	260 (94.9)	0.03
HSV-1 seronegative	2 (14.3)	12 (85.7)	14 (5.1)	
	Stillbirths			
	Yes (*n*=13)	**No (*n*=261)**	**Total tested (*n*=274)**	
HSV-1 seropositive	12 (4.6)	248 (95.4)	260 (94.9)	0.50
HSV-1 seronegative	1 (7.1)	13 (92.9)	14 (5.1)	

LBW=Low birth weight; HSV=Herpes simplex virus

Occurrence of complications: Incident herpes simplex virus-2 infection versus HSV-2 seronegative groups

There was an increased risk of occurrence of LBW delivery, preterm delivery, and stillbirths among cohorts with incident HSV-2 infection relative to those who did not seroconvert (relative risk [RR] =12.6 [95% CI: 9.8–16.4]), (RR = 25.1 [95% CI: 23.9–26.3]), and (RR = 4.5 [95% CI: 3.5–4.5]), respectively. The RR of occurrence of spontaneous abortion among the group with incident HSV-2 infection was found to be extremely high [Table 6].

Effect of HSV-1 antibodies on pregnancy outcomes in the "incident HSV-2 infection" group: Only 1 (5.9%) of the 17 participants in the "incident HSV-2 infection group" was HSV-1 seronegative and so had primary first episode infection. This implies that the majority (94.1%) of them had nonprimary first-episode infection.

Data do not indicate any significant influence of HSV-1 serostatus on the occurrence of LBW delivery, spontaneous abortion, preterm delivery, and stillbirths ($P = 1.0$, 1, 0.353, and 1, respectively). This suggests a lack of the protective effect of preexisting HSV-1 antibodies on outcome of incident HSV-2 infection in pregnancy [Table 7].

Effect of HSV-1 antibodies on pregnancy outcomes in the "HSV-2 seropositive" group: The 17 HSV-seronegative participants in this study were distributed among the "HSV-2 seropositive," "HSV-2 seronegative" and the "incident HSV-2 infection" groups in the following pattern: 14 (5.1%) versus 3 (1.1%) and 1 (5.9%), respectively [Figure 1].

The "HSV-2 seropositive group" contains the greatest number of HSV-1 seronegative participants, relative to the other groups and is, therefore, useful in studying the influence of HSV-1 antibodies on incidence of complications.

There were higher prevalences of LBW deliveries, preterm deliveries, and stillbirths among HSV-1 seronegative participants compared to their HSV-1 seropositive counterparts. However, the differences in occurrence of LBW delivery and stillbirths were not statistically significant ($P = 0.27$ and $P = 0.5$, respectively); while that of preterm delivery was significant ($P = 0.03$) [Table 8].

Discussion

The characteristics of the participants who completed the follow-up protocols were similar to those of the baseline study population. We could, therefore, assume that the factors that could influence the outcome of pregnancy in the baseline study population were also present in the follow-up study population. We also assumed that the factors other than HSV-2 statuses were randomly distributed.

The 46.3% HSV-2 seroprevalence value found in this study population is high though it is still within the range estimated to be typical of sub-Saharan African women of reproductive age.[13]

Our HSV-2 seroconversion frequency of 5.6% found among those who were HSV-2 seronegative at baseline is much higher than the 1.7% found among HSV-2 seronegative USA women who had preexisting HSV-1 antibodies (a characteristic of this study population).[2] The high seroconversion frequency found in this study population conforms to the high 2003 World Health Organization estimate on genital herpes incidence rate in sub-Saharan Africa.[13]

Furthermore, our finding of significant association of incident HSV-2 infection with increased chance of occurrence of LBW deliveries, preterm deliveries, stillbirths, and spontaneous abortions is in agreement with previous reports from USA.[3-7]

To our knowledge, this is the first study on the effects of HSV-2 infection on outcome of pregnancy in Nigeria. Consequent on paucity of study reports assessing the burden of HSV-2 infection in pregnancy in Nigeria and Africa,[13] it is difficult to effect comparisons or assess trends. However, with such a high seroconversion frequency, which indicates high transmission efficiency, it is certain that the burden of HSV-2 infection may be on the rise.

According to our findings, and in keeping with previous reports,[14] HSV-2 infections acquired before the pregnancy are associated with only a low risk of occurrence of obstetric complications. Thus, there was no statistically significant difference in the occurrence of the complications between the "HSV-2 seropositive" group and the "HSV-2 seronegative" group. This finding agrees with reports from a retrospective study in Korea,[14] and can be explained by the presence of HSV-2 specific antibodies which can protect the fetus from the severe effects of maternal HSV-2 infection.[3] With respect to spontaneous abortion, no such complication was recorded in both "HSV-2 seropositive" and "HSV-2 seronegative" groups. This is contrary to the report from Korea in which significantly more spontaneous abortions occurred among the HSV-2 seropositive persons.[14] The low frequency of spontaneous abortion in this study population may have resulted from the low proportion of the first trimester enrollees, which is a reflection of the tendency of pregnant women in this environment to book late. Moreover, due to the bitterness associated with pregnancy loss in this environment, it is possible that a significant proportion of those who were lost to follow-up had this complication.

Just as the presence of HSV-2 specific antibodies can protect the fetus, the absence of HSV-2 specific antibodies may

make the fetus vulnerable to the first episode infections. This may explain why the first episode maternal HSV-2 infections (whether primary or nonprimary) in pregnancy were associated with higher frequency of occurrence of LBW deliveries, stillbirths, and preterm deliveries in this study. Even spontaneous abortion, which was absent in the other cohorts, was present in the "incident HSV-2 infection" cohort. This agrees with previous reports on the effects of the first episode HSV-2 infection on obstetric outcome.[3-7] Contrary to this finding, another previous prospective study in USA reported no significant increase in the negative outcomes of pregnancy among "incident HSV-2 infection" participants, relative to other cohorts.[2] The reason for this difference in research finding may be due to the fact that in advanced countries of the world like USA, there is better health facilities, that ensures better management of pregnant women than in third world countries; this helps reduce the morbidity and mortality associated with all forms of infections, including HSV in advanced countries of the world.

There was zero occurrence of the, so-called, most devastating complications, namely neonatal herpes and congenital malformations, among this study population. However, based on results of a survey in USA, these events are rare and occur at the rate of 1: 3000–20,000.[15] The nonoccurrence of neonatal herpes, in this study, could also be attributable to other factors. We found that none of the 3rd trimester enrollees seroconverted; and this implies that incident HSV-2 infection in this population is very unlikely to have occurred. Since it is known that neonatal herpes is a consequence of incident HSV infections occurring near term, the nonincidence of neonatal herpes could also be attributable to this possible lack of incident HSV-2 infection near term. The zero seroincidence of HSV-2 infection among the third trimester enrollees may be related to the cultural practice of markedly reduced/absent sexual activity at late pregnancy.[2,13]

However, the use of antibody detection as the basis of incident HSV-2 infection is one limitation of this study. This implies that infections occurring less than 3 weeks to delivery date may have been missed because there could not have been detectable seroconversion.[16] It should be noted, however, that none of the participants enrolled at later than 28 weeks gestational age. If there are cultural restrictions to sex at late pregnancy, when the woman is said to be "heavy," the restrictions should be tighter at 3 weeks to delivery.

The absence of severe complications like neonatal herpes should not, in any way, reduce the seriousness of HSV-2 infection in pregnancy. We think that spontaneous abortions and stillbirths are as serious as neonatal herpes; and these complications can occur at any gestational age. The focus on near-term prevention of maternal-to-fetal-transmission of HSV-2 seems to be the result of excessive focus on neonatal herpes. The adequacy of this approach requires re-assessment. This is due to the fact that first episode (primary or nonprimary) maternal infections do occur any time in the pregnancy; and is even more likely to occur earlier in the pregnancy, as in this study. Contrary to previous reports,[2,17] we found distinct associations of incident HSV-2 infections with fetal loss, either as stillbirths or spontaneous abortions. The fact that about a quarter of the stillbirths were macerated testifies to possible lethal fetal events. This possible lethal effect of incident HSV-2 infection can be explained by the high level of primary viremia, and the initial lack of specific antibodies which is associated with any natural HSV-2 infection.[18,19] The possibility of other, "nonlethal," events was also highlighted by this study. Although all the preterm delivery and LBW babies thrived well on postnatal clinic follow-up visit, the negative effects of these obstetric outcomes on child survival – on public health scale – are well-known.[20]

Based on a study report on the protective effect of antibodies,[21,22] it is widely believed that heterologous (HSV-1) antibodies are protective. The results of the analysis of the pattern of complications in the "HSV-2 seropositive" group provide evidence of some protective effect of heterologous antibodies. As complications in the "HSV-2 seropositive" group persons result from recurrences, the presence of both HSV-1 and HSV-2 antibodies is expected to provide some protection from the effects of viremia. Thus, there was increased prevalence of complications in the HSV-1 seronegative members of the "HSV-2 seropositive" group, although statistical significance was achieved only with respect preterm delivery.

On the other hand, considering first episode HSV-2 infections, our findings readily suggest that the protective effect of preexisting HSV-1 antibodies is negligible. Majority (94.1%) of the first episode infections were of nonprimary type (occurred in association with preexisting HSV-1 antibodies); and it has already been noted that most of the complications, in this study, were associated with first episode infections. However, as a result of the 96.3% seroprevalence of HSV-1 in this study population (compare 57.7% in USA),[23] it is difficult to do a comparative assessment of the effect of HSV-1 on the occurrence of the complications, with this limited number of participants in an "incident HSV-2 infection" group in which only 1 of 17 members was HSV-1 seronegative.

Furthermore, it could be thought that the failure of several candidate HSV-2 vaccines in HSV-1 seropositive subjects could imply reasonable protection of the subjects from the HSV-2-associated pathologies.[24] Our findings indicate that the protection is limited and may be negligible in the first episode infections. Thus, despite the discouraging effect of HSV-1 antibodies on vaccine development efforts, vaccine research should be intensified. Focus should be placed on

developing candidate vaccines that can induce immunity in HSV-1 seropositive individuals.

This study further demonstrates that HSV-2 infection burden among the pregnant women in Nigeria is high. The burden is on the rise, and the associated complications could be alarming. Community-based surveys are required to ascertain these findings on a wider scale. This would form the baseline for designing interventions to prevent morbidities and mortalities associated with the infection in third world countries.

Conclusion

First episode HSV-2 infection among pregnant women in sub-Saharan African countries like Nigeria (Benin) is associated with an increased risk of occurrence of spontaneous abortion, LBW delivery, and preterm delivery.

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