

Seroprevalence and Factors Associated with Risk of Hepatitis B Virus Infection among Antenatal Attendees in ABUTH Zaria, Northwestern Nigeria

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Abstract

Background: Nigeria is one of the sub-Saharan African countries within the World Health Organization's (WHO) hyperendemic region for hepatitis B virus infection with prevalence greater than 8%. In this region, mother-to-child transmission is the major route of infection and approximately 90% of newborns of mothers who are seropositive for HBsAg and HBeAg become chronic carriers with a 25% risk of developing chronic liver diseases. This study aimed to determine the seroprevalence, and factors associated with risk of hepatitis B virus infection among antenatal attendees in Ahmadu Bello University Teaching Hospital (ABUTH), Zaria.

Methodology: A hospital based cross sectional study was conducted among pregnant women attending the antenatal booking clinic of ABUTH, Zaria from August 2017 to January 2018. Systematic random sampling was used. An interviewer administered questionnaire was used to obtain data on sociodemographic characteristics and risk factors for HBV infection. Blood samples were collected and tested using the third generation ELISAKIT for HBsAg (Monolisa HBsAg ULTRA BIORAD, France) and HBeAg (HBeAg & Ab, DiaPro Diagnostic Bioprobes Milano Italy). Data were analyzed using SPSS version 20 (IBM USA, 2011). Statistical testing was carried out with chi-square and level of significance set as $P < 0.05$.

Results: The mean age of the respondents was 26 ± 6.1 years, the highest HBV seropositivity occurred in the age group 21-25 years from a total of 192 participants. The seroprevalence of HBV obtained was 15.1%. Only 1 (3.4%) woman was positive for HBeAg among the 29 HBsAg seropositive women. Past history of unsafe injections was the only risk factor significantly associated with HBV seropositivity ($\chi^2 = 5.628$, p -value = 0.023).

Conclusions: The seropositivity of hepatitis B virus was high among pregnant women. Interventions targeted at injection safety will help reduce the risk of infection.

Keywords: Hepatitis B Virus (HBV); Pregnant Women; Antenatal Clinic; Ahmadu Bello University Teaching Hospital, Zaria.

Introduction

Hepatitis B virus infection is a very important global public health problem. An estimated two billion people are affected worldwide, over 360 million have chronic liver infections, 240 million

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have active infection and 10-30 million will become infected each year. Nigeria like other countries in sub-Saharan Africa falls within the World Health Organization's (WHO) hyperendemic region for hepatitis B virus infection. In this region, the usual mode of transmission is from mother-to-child (MTCT) at the time of birth from a chronically infected mother. The risk of MTCT is related to maternal and viral factors including antepartum haemorrhage, premature rupture of membranes, Hepatitis B e antigen (HBeAg) seropositivity, viral load {HBV DNA level $\geq 10^6$ copies/mL ($>200\ 000$ IU/mL)} etc.

Approximately 90% of infants of HBsAg and HBeAg seropositive mothers in hyper endemic areas become HBsAg chronic carriers, while for HBeAg negative mothers, the rate is between 10-40%. Almost 25% of individuals who become chronically infected during infancy and childhood die from HBV-related liver cancer or cirrhosis later in life.

This study aimed to determine the seroprevalence and factors associated with risk of hepatitis B viral infection among antenatal attendees in Ahmadu Bello University Teaching Hospital (ABUTH), Zaria.

Materials and Methods

This study was carried out in Ahmadu Bello University Teaching Hospital (ABUTH), a tertiary health care centre located in Zaria, one of the major towns in Kaduna state, northwestern Nigeria. It is a 500 bedded hospital which serves as referral centre for patients within Kaduna and from neighbouring states. The department of Obstetrics and Gynaecology runs antenatal clinics on Mondays to Fridays and booking of new cases is done every Wednesday of the week.

It was across-sectional study of pregnant women that presented for booking every Wednesday at the antenatal clinic of ABUTH teaching hospital Zaria.

The inclusion criteria were pregnant women aged 16-50 years that had not received vaccine against hepatitis B virus. Those who had been diagnosed of HBV infection or declined consent were excluded.

The sample size estimation was determined based on a prevalence of 13.3%. The participants were selected using systematic random sampling technique on every booking day over a period of 24 weeks from the month of August 2017 to January 2018. A structured interviewer-administered questionnaire in English and translated to the local dialect (Hausa) with two sections (A & B) was used. Section A was designed to document the socio-demographic data of women and section B was for risk factors of HBV infection acquisition.

About 4 milliliter of blood sample was aseptically collected by venepuncture from each participant into a labeled sterile plain bottle and subsequently transported to the laboratory. The serum from each sample was separated, pooled then screened for HBsAg and HBeAg every week. Standard precaution was ensured during samples handling. All test kits manuals and inserts were followed strictly according to the manufacturer's instructions.

Screening

All samples collected were screened for HBsAg with a third generation ELISA kit (Monolisa HBsAg ULTRA, BIORAD- France). The samples positive for HBsAg were subjected to further testing for HBeAg with another third generation ELISA kit (HBeAg & Ab DIAPRO diagnostic, Bioprobes Milano-Italy).

Data management

Data were subjected to descriptive and inferential statistics. Results are presented in tables and charts. Analysis was carried out using the Statistical Package for Social Sciences (SPSS) version 20 (IBM USA, 2011). Relationship between variables was determined using chi-square and level of significance was considered at $p < 0.05$.

Ethical consideration

Ethical approval was obtained from the Health Research ethics Committee of the ABUTH. Permission was obtained from the Head, Department of Obstetrics and Gynaecology. Written and informed consent in English/Hausa were obtained from each participant as applicable.

Result

A total of 192 pregnant women participated in this

study. The mean age was 26.0±6.1SD. The predominant tribe was Hausa 155(80.7%). The dominant religion was Islam 171(89.1%). One hundred and ninety of the respondents (99.0%) were married and those in monogamous setting constituted 159(83.2%). Those with tertiary education constituted about a half 87(45.5%) while 7(3.7%) had non-formal Quranic education. About a half of the women were house wives 91(47.4%), while only 39(20.3%) were employed in the formal sector. Almost all the participants were residents of Zaria 172(89.6%). About a quarter of them 53(27.6%) were pregnant for the first time and approximately half of them 100(52.1%) were in their second trimester. This is shown in table 1.

Among the 192 participants, HBsAg was detected in 29(15.1%) of them. Of these HBsAg seropositive pregnant women, only 1(3.4%) was positive for HBeAg. This is shown in figure 1.

Of the 78 respondents who had history of unsafe injection in the past, 6(7.7%) were positive for the HBsAg. There was a statistically significant association between unsafe injection on one hand and HBV acquisitions on the other hand ($\chi^2 = 5.628$ p-value= 0.023). However, history of blood transfusions, previous contact with known HBV infected patients, multiple sex partners, and other risk factors assessed were not significantly associated with the acquisition HBV infection in this study. This is shown in table 2.

Table 1: Sociodemographic characteristics of studied participants at ANC of ABUTH, Zaria

Variables	Frequency, n=192	%
Age		
16-20	25	13
21-25	71	37
26-30	47	24.5
31-35	21	16.1
..	18	9.4
Ethnic Group		
Hausa/Fulani	155	80.7
Yoruba	8	4.2
Igbo	3	1.6
Others	26	13.5

Religion		
Christianity	21	10.9
Islam	171	89.1
Marital status		
Married	190	99
Single	2	1
Employment Status		
Employed	39	20.3
Unemployed	22	11.5
self employed	12	6.3
house wife	91	47.4
Student	27	14.1
Others	1	0.5
Family Setting		
Monogamous	107	82.3
Polygamous	22	16.9
single mother	1	0.8
Residence		
Within Zaria	172	89.6
Outside Zaria	20	10.4
Gravidity		
1	53	26.6
2	36	18.7
3	55	17.2
4	24	12.5
5 or more	46	24
Gestational age		
0-3month	21	10.9
4-6month	100	52.1
7-9month	71	37

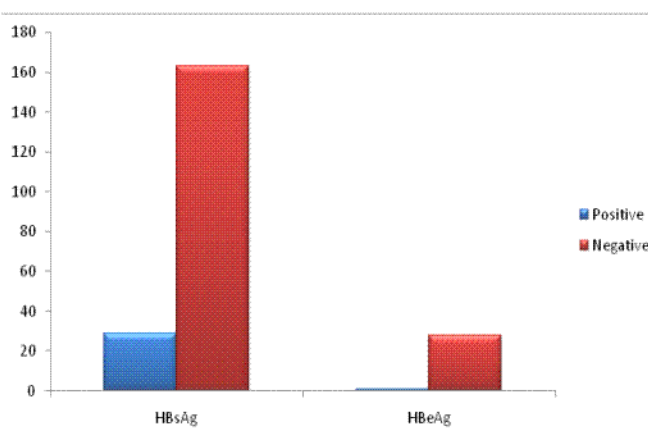


Figure 1: Seroprevalence of HBsAg and HBeAg of ANC attendees of ABUTH Zaria

Table 2: Association between selected risk factors and HBsAg status of ANC attendees of ABUTH Zaria

	HBsAg Reaction		X ²	P-value
	Positive n (%)	Negative n (%)		
Gravidity				
1	8 (27.6)	45(26.8)	1.711	0.803
2	7 (24.1)	29(17.8)		
3	4 (13.8)	29(17.8)		
4	2 (6.9)	22(13.5)		
5 or more	8 (27.6)	38(23.3)		
Total	29 (100)	163(100)		
Contact with HBV infected person				
Yes	4 (13.8)	11 (6.8)	2.007	0.238
No	25 (86.2)	152(93.2)		
Total	29 (100)	163 (100)		
Surgical procedure				
Govt. hospital	2 (67.7)	9 (90.0)	3.246	0.423
Private hospital	0 (0.0)	1 (10.0)		
Other places	1 (33.3)	0 (100)		
Total	3 (100)	10 (100)		
Scarification mark				
Yes	1 (3.4)	10 (6.1)	0.329	1.000
No	28 (96.6)	153 (93.9)		
Total	29 (100)	163 (100)		
Female circumcision				
Yes	1 (3.4)	8 (4.9)	0.117	1.000
No	28 (96.6)	155 (95.1)		
Total	29 (100)	163 (100)		
Uvulectomy				
Yes	9 (31)	51(31.3)	0.001	1.000
No	20 (69)	112 (68.9)		
Total	29 (100)	163 (100)		
Blood transfusion				
Yes	2 (6.9)	21 (12.9)	0.873	0.538
No	27 (93.1)	142 (87.1)		
Total	29 (100)	163 (100)		
Life time sex partner				
1	25 (82.2)	147 (90.2)	1.873	0.640
2	4 (13.8)	15 (9.2)		
3	0 (0.0)	1 (0.6)		
Total	29 (100)	163 (100)		

	HBsAg Reaction		X ²	P-value
	Positive n (%)	Negative n (%)		
Does husband has other wives				
Yes	6 (20.7)	37 (22.7)	0.065	1.000
No	23 (79.3)	126 (77.3)		
Total	29(100)	163 (100)		
Distance journey Husband				
Yes	3 (10.3)	20 (12.3)	0.093	1.000
No	26 (89.7)	142 (87.7)		
Total	29 (100)	162 (100)		
Age at first sexual exposure				
<15	1 (3.4)	11(6.7)	2.141	0.694
16-20	11 (37.9)	72 (44.2)		
21-25	14 (48.3)	67 (41.1)		
26-30	2 (6.9)	11 (6.7)		
Above 30	1 (3.4)	2 (1.2)		
Total	29 (100)	163 (100)		
Past unsafe injections	Positive	Negative		
Yes	6 (20.7)	72 (44.2)	5.628	0.023 ^a
No	23 (79.3)	91 (55.8)		
Total	29 (100)	163 (100)		

^aSignificance

Discussion

The seroprevalence of HBsAg positivity obtained from this study was 15.1%. This prevalence was comparable to 13.3% reported by Jatau *et al* among pregnant women attending antenatal clinic in Ahmadu Bello University Medical Centre Zaria in 2014. However, this finding was higher than 8.3% reported by Luka *et al* in 2008 among antenatal clients in the same facility where this study was carried out. It was also higher than the prevalence reported from other parts of the country: 7.9% reported in Kano by Yakasai *et al*, 12.3% reported in Minna by Ndams *et al*, 8.2% reported by Olokoba *et al* in Yola, 8.3% reported in Ibadan by Anaedobe *et al* and 6% reported by Lu *et al* in Nnewi. All studies were conducted among antenatal clients in public hospitals in Nigeria. The prevalence obtained seems to be increasing from the southern to the northern

part of the country as earlier reported by Mbaawuaga *et al*. The disparities in prevalence obtained from most of these studies may be due to the assay methods employed, the study period and geographical location. For most of the studies, rapid diagnostic kits were mainly used which are not as sensitive or specific compared to the ELISA that was used in this study. Other factors which may explain these disparities are the health seeking behaviour which is related to the level of education, awareness and socio-economic status of the participants. Women in the southern part of this country are more educated and independently tend to seek healthcare freely more than their northern counterparts. Polygamy and early age at marriage which are common practices in the northern part may also account for the high value obtained in this study.

The seroprevalence obtained value (15.1%) showed that this area like other parts of the country is highly endemic for hepatitis B virus. This agrees with the WHO [1990] report that countries in sub-Saharan Africa are hyperendemic for hepatitis B virus, with seroprevalence greater than 8%. This finding was also in conformity with reports by Kirre *et al*; that sub-Saharan Africa has a HBV carrier rate of between 9-20%. However, the prevalence was higher than values from similar studies done in other sub-Saharan Africa countries including Uganda; northern Cameroon and eastern Ghana. This finding compared to studies carried out in other parts of the world, doubled the figure reported from parts of China and the United states. It was also much higher than reports from Hong Kong and Taiwan. This prevalence was however lower than reports of a study conducted in Burkina Faso; and even much lower than that obtained in a subgroup of individuals such as HBV infected female sex workers in Nigeria and among intravenous drug abusers in Pakistan. The endemic pattern of HBV in different geographical locations and sample sizes analyzed may contribute to the disparities in prevalence reported from these studies.

Of the 29 seropositive pregnant women, the highest value 13(44.8%) occurred within the age group of 21-25years. This is in keeping with findings from studies conducted in Minna and Benue state *but different from* that reported in Ibadan which got the

highest value among participants in the age group of 29-35years. These findings may be related to the age of marriage by the participants, as women in the northern part of the country marry at earlier ages than their counterparts in the south. The seropositivity was also highest for pregnant women in their second trimesters n(17%) followed by those in their third trimester n(14%). This is comparable to the findings of studies done in Kano and Minna in which pregnant women in their second trimesters had the highest prevalence of 10.2% and 13.4% followed by 5.6% and 7.8% in those in their third trimesters respectively. These findings can be explained by the gestational age at booking by the participants in this study as most of them 100(52.1%) commenced antenatal visit in the second trimester.

The prevalence of HBeAg among the carriers was 3.4%, which means that approximately one in every fifty subjects (0.5%) in the entire studied population is capable of transmitting the virus to their newborns. This prevalence rate is comparable to 0.8% reported in Zimbabwe but lower than 1.39% and 3.3% reported in Maiduguri and Makurdi *respectively*. The high prevalence of HBsAg and low HBeAg obtained from this study signified that HBV infection transmission was more likely to be through horizontal than the vertical route.

Among the selected known risk factors for HBV acquisition in this study, previous usage of unsafe injection was found to be associated with the likelihood of infection and accounted for 7.7%. Unsafe injection in this context implies receiving injection from unqualified healthcare providers outside healthcare facilities. It also include unsafe practices such as multiple injections using single needle/syringe, multiple draws from single vials for different patients, giving injections without skin disinfection and giving injection over the clothes which are common practices by quacks that abounds in rural communities of sub-Saharan Africa.

Conclusion

The seroprevalence of HBV obtained in this study was 15.1%. This finding was highest for pregnant women in the second trimester and those in the age group of 21-25years. However, the seropositivity of HBeAg was relatively low (3.4%) indicating a

reduced risk of vertical transmission. Previous use of unsafe injection was found to be a risk factor for the acquisition of HBV.

Recommendation

All Pregnant women should be screened for HBsAg at antenatal booking and those found positive should also be tested for HBeAg. All seropositive mothers should be managed appropriately to prevent vertical transmission and the negative ones should be encouraged to get vaccinated after delivery. Health information on safe injection use should be emphasized to pregnant women during antenatal visits to health facilities.

References

- Ikobah J, Okpara H, Elemi I, Ogarepe Y, Udoh E, Ekanem E. The prevalence of hepatitis B virus infection in nigerian children prior to vaccine introduction into the national programme on immunization schedule. *Pan Afr Med J* 2016; **23**:128.
- Stanaway JD, Flaxman AD, Naghavi M, Fitzmaurice C, Vos T, Abubakar I, et al. The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. *Lancet*. 2016; **388**:10049.
- Flores A, Marrero JA. Emerging trends in hepatocellular carcinoma: focus on diagnosis and therapeutics. *Clin Med Insights Oncol* 2014; **8**:71-6.
- Nelson NP, Jamieson DJ, Murphy T V. Prevention of Perinatal Hepatitis B Virus Transmission. *J Pediatric Infect Dis Soc* 2014; **3** (suppl_1):S7-12.
- Li Z, Hou X, Cao G. Is mother-to-infant transmission the most important factor for persistent HBV infection? *Emerg Microbes Infect* 2015; **4**:e30.
- Franco E, Bagnato B, Marino MG, Meleleo C, Serino L, Zaratti L. Hepatitis B: Epidemiology and prevention in developing countries. *World J Hepatol* 2012; **4**:74-80.
- Cochran WG. Sampling Technique, 3rd Edition. 1977; John Wiley&Sons. *New York, USA*: 89-99.
- Jatau E., Yabaya A. Sero prevalence of Hepatitis B Virus in pregnant women attending a clinic in Zaria, Nigeria. *Sci World J* 2010; **4**:7-9.
- Luka SA, Ibrahim M, Iliya S. Sero-prevalence of hepatitis B surface antigen among pregnant women attending Ahmadu Bello University Teaching Hospital, Zaria, Nigeria. *Niger J Parasitol* 2008; **29**:38-41.
- Yakasai I, Ayyuba R, Abubakar I, Ibrahim S. Sero-prevalence of Hepatitis B Virus Infection and its Risk factors among Pregnant Women Attending Antenatal Clinic at Aminu Kano Teaching Hospital, Kano, Nigeria. *Journal of Basic and Clinical Reproductive Sciences* 2012; **(1-2)**:49-55.
- Ndams IS, Joshua IA, Luka SA, Sadiq HO. Epidemiology Of Hepatitis B Infection Among Pregnant Women In Mina, Nigeria. *Sci World J* 2008; **3**:5-8.
- Olokoba AB, Salawu FK, Danburam A, Olokoba LB, Midala JK, Badung LH, et al. Hepatitis B virus infection amongst pregnant women in North-Eastern Nigeria - A call for action. *Niger J Clin Pract*. 2011; **14**:10-3.
- Anaedobe CG, Fowotade A, Omoruyi CE, Bakare RA. Prevalence, sociodemographic features and risk factors of Hepatitis B virus infection among pregnant women in Southwestern Nigeria. *Pan Afr Med J* 2015; **20**:406.
- Oluboyo B, Ugochukwu V, Oluboyo A, Ihim A, Chukwuma G, Ogenyi S, Onyemelukwe A. Prevalence Of Hepatitis B And C Viral Infections In Pregnant Women Attending Antenatal Clinic In Nnewi, Nigeria. *ESJ* 2014J;**10**
- Mbaawuaga E., Enenebeaku M, Okopi J, Okopi J. Hepatitis B Virus (HBV) infection among pregnant women in Makurdi, Nigeria. *African J Biomed Res* 2008; **11**:154-159.
- Erhabor O, Kwaifa IK, Bayawa AM, Isaac ZI, Bosede DI, Sani I. Comparison of ELISA and Rapid Screening Techniques for the Detection of HBsAg among Blood Donors in Usmanu Danfodiyo University Teaching Hospital Sokoto, North Western Nigeria. *J Blood Lymph* 2014; **4**:124.
- Csapo M. Religious, Social and Economic Factors Hindering the Education of Girls in Northern Nigeria, *Comparative Education* 1981;**17**:311-319.

18. Erulkar A, Bello M. The experience of married adolescent girls in Northern Nigeria." Abuja: Population Council 2007.doi:10.31899/pgy17.1022.
19. Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. *Vaccine* 2012; **30**:2212-9.
20. Kiire CF. The epidemiology and prophylaxis of hepatitis B in sub-Saharan Africa: a view from tropical and subtropical Africa. *Gut* 1996; **38**(Suppl 2):S5-12.
21. Bayo P, Ochola E, Oleo C, Mwaka AD. High prevalence of hepatitis B virus infection among pregnant women attending antenatal care: a cross-sectional study in two hospitals in northern Uganda. *BMJ Open* 2014; **4**:e005889.
22. Frambo AAB, Atashili J, Fon PN, Ndumbe PM. Prevalence of HBsAg and knowledge about hepatitis B in pregnancy in the Buea Health District, Cameroon: a cross-sectional study. *BMC Res Notes* 2014; **7**:394.
23. Luuse A, Dassah S, Lokpo S, Ameke L, Noagbe M, Adataro P, et al. Sero-prevalence of Hepatitis B surface antigen amongst pregnant women attending an antenatal clinic, Volta region, Ghana. *J Public Health Africa* 2016; **7**:584.
24. Ding Y, Sheng Q, Ma L, Dou X. Chronic HBV infection among pregnant women and their infants in Shenyang, China. *Virol J.* 2013; **17**:1-5.
25. Dunkelberg JC, Berkley EMF, Thiel KW, Leslie KK. Hepatitis B and C in pregnancy: a review and recommendations for care. *J Perinatol* 2014; **34**:882-91.
26. Tong S, Kim KH, Chante C, Wands J, Li J. Hepatitis B Virus e Antigen Variants. *Int J Med Sci.* 2005; **2**:2-7. doi:10.7150/ijms.2.2
27. Lin H-H, Kao J-H, Chang T-C, Hsu H-Y, Chen D-S. Secular trend of age-specific prevalence of hepatitis B surface and e antigenemia in pregnant women in Taiwan. *J Med Virol* 2003; **69**:466-70.
28. Collenberg E, Ouedraogo T, Ganamé J, Fickenscher H, Kynast-Wolf G, Becher H, et al. Seroprevalence of six different viruses among pregnant women and blood donors in rural and urban Burkina Faso: A comparative analysis. *J Med Virol* 2006; **78**:683-92.
29. Forbi JC, Onyemauwa N, Gyar SD, Oyeleye AO, Entonu P, Agwale SM. High prevalence of hepatitis B virus among female sex workers in Nigeria. *Rev Inst Med Trop Sao Paulo* 2008; **50**:219-21.
30. Alam MM, Zaidi SZ, Shaukat S, Sharif S, Angez M, Naeem A, et al. Common genotypes of Hepatitis B virus prevalent in injecting drug abusers (addicts) of North West Frontier Province of Pakistan. *Virol J* 2007; **4**:63.
31. Madzime S, Adem M, Mahomed K, Woelk GB, Mudzamiri S, Williams MA. Hepatitis B virus infection among pregnant women delivering at Harare Maternity Hospital, Harare Zimbabwe, 1996 to 1997. *Cent Afr J Med* 1999; **45**:195-8.
33. Harry TO, Bajani MD, Moses AE. Hepatitis B virus infection among blood donors and pregnant women in Maiduguri, Nigeria. *East Afr Med J* 1994; **71**:596-7.
34. Singh J, Bhatia R, Patnaik SK, Khare S, Bora D, Jain DC, et al. Community studies on hepatitis B in Rajahmundry town of Andhra Pradesh, India, 1997-8? unnecessary therapeutic injections are a major risk factor. *Epidemiol Infect* 2000; **125**:367-75.
35. Simonsen L, Kane A, Lloyd J, Zaffran M, Kane M. Unsafe injections in the developing world and transmission of bloodborne pathogens: a review. *Bull World Health Organ* 1999; **77**:789-800.