HBV detection in pregnancy: rapid tests or ELISA?  

Fowotade et al. Afr. J. Clin. Exper. Microbiol. 2021; 22 (3): 352 - 358  
https://www.africem.org

African Journal of Clinical and Experimental Microbiology. ISSN 1595-689X  
AJCEM/2125. https://www.africa.info/index.php/ajcem  
Jul 2021; Vol.22 No.3

Copyright AJCEM 2021: https://dx.doi.org/10.4314/ajcem.v22i3.6

Original Article

Hepatitis B virus infection among pregnant women on antenatal visits: rapid tests or ELISA?

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Abstract:

Background: Hepatitis B virus (HBV) infection is a global public health challenge with over 360 million people infected worldwide, and is one of the leading causes of death worldwide. The hepatitis B surface antigen (HBsAg) is the most important marker for HBV screening, and HBsAg rapid screening test methods are the most widely used compared with the enzyme-linked immunosorbent assay (ELISA) and nucleic acid testing methods. The objectives of this study are to evaluate the comparative efficacy of rapid test kits and ELISA for HBV screening among pregnant women on antenatal visits and to screen for other HBV serological markers among HBsAg positive patients.

Methodology: This is a cross-sectional study of 172 pregnant women who were recruited consecutively on their first antenatal visit at the University College Hospital, Ibadan, Nigeria between November 2018 and February 2019. All participants were screened for HBsAg using both rapid immunochromatographic test (ICT) and ELISA techniques. HBsAg negative samples were further screened for anti-HBeAg/Ab, anti-HBcAg and anti-HBs by ELISA. Socio-demographic data of the participants were obtained using a semi-structured questionnaire, and data were analyzed using EPI INFO 7.2 statistical software.

Results: The prevalence rate of HBsAg among pregnant women in this study was 10.5% (18/172). The sensitivity, specificity, accuracy, positive predictive value (PPV) and the negative predictive value (NPV) of the rapid ICT kit were 72.2%, 97.4%, 94.8%, 76.5% and 96.8% respectively. Level of education, previous history of sexually transmitted infections (STIs) and previous positive HBV results were significantly associated with HBsAg seropositivity. Majority of the pregnant women (66.9%) tested negative to all the serological markers.

Conclusion: The low efficacy of rapid ICT kits compared to ELISA justifies the need to develop a safer antenatal screening strategy for HBV by combining the use of the less sensitive rapid screening techniques with the more sensitive ELISA method to limit vertical transmission of hepatitis B virus.

Keywords: Hepatitis B virus; Rapid ICT kits; ELISA; pregnant women

Received May 10, 2021; Revised May 25, 2021; Accepted May 26, 2021

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Infection par le virus de l’hépatite B chez les femmes enceintes en consultation prénatale: tests rapides ou ELISA?

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Abstrait:

Contexte: L’infection par le virus de l’hépatite B (VHB) est un défi de santé publique mondial avec plus de 360 million de personnes infectées dans le monde et est l'une des principales causes de décès dans le monde. L’antigène de surface de l’hépatite B (HBSAg) est le marqueur le plus important pour le dépistage du VHB, et les méthodes de test de dépistage rapide HBSAg sont les plus largement utilisées par rapport aux méthodes de test immuno-enzymatique (ELISA) et d’acide nucléique. Les objectifs de cette étude sont d'évaluer l'efficacité comparative des kits de tests rapides et de l’ELISA pour le dépistage du VHB chez les femmes enceintes lors de consultations prénatales et de dépister d’autres marqueurs sérologiques du VHB chez les patients AgHBs positifs.

Méthodologie: Il s’agit d’une étude transversale de 172 femmes enceintes qui ont été recrutées consécutivement lors de leur première visite prénatale à l’Hôpital Universitaire, Ibadan, Nigéria entre novembre 2018 et février 2019. Tous les participants ont été dépistés pour l’AgHBs en utilisant les deux tests immuno-chromatographiques rapides (TIC) et techniques ELISA. Les échantillons négatifs à l’AgHBs ont en outre été criblés pour l’anti-HBeAg/Ab, l’anti-HBcAg et l’anti-HBs par ELISA. Les données sociodémographiques des participants ont été obtenues à l’aide d’un questionnaire semi-structuré et les données ont été analysées à l’aide du logiciel statistique EPI INFO 7.2.

Résultats: Le taux de prévalence de l’HBSAg chez les femmes enceintes dans cette étude était de 10,5% (18/172). La sensibilité, la spécificité, la précision, la valeur prédictive positive (VPP) et la valeur prédictive négative (VPN) du kit ICT rapide étaient respectivement de 72,2%, 97,4%, 94,8%, 76,5% et 96,8%. Le niveau d’éducation, les antécédents d’infections sexuellement transmissibles (IST) et les résultats positifs antérieurs pour le VHB étaient significativement associés à la séropositivité de l’AgHBs. La majorité des femmes enceintes (66,9%) ont été testées négatives pour tous les marqueurs sérologiques.

Conclusion: La faible efficacité des kits TIC rapides par rapport à l’ELISA justifie la nécessité de développer une stratégie de dépistage prénatal plus sûre du VHB en combinant l’utilisation des techniques de dépistage rapide moins sensibles avec la méthode ELISA plus sensible pour limiter la transmission verticale du virus de l’hépatite B.

Mots clés: virus de l’hépatite B; Kits TIC rapides; ELISA; femmes enceintes.

Introduction:

Chronic hepatitis B virus (HBV) infection is the most common cause of liver cirrhosis and hepatocellular carcinoma (1). Vertical transmission of HBV is the most common cause of chronic HBV infection and is a public health concern in endemic regions, such as the Far East and Africa (2-5). The first detectable antigen in the course of HBV infections is the HBSAg whose presence often predates the appearance of symptoms in clinically ill patients. An identifiable viral core antigen (HBcAg) exists but does not circulate free in serum like HBSAg. A third antigen, the e antigen (HBeAg), is associated primarily with the core antigen in the internal structure of the virus, and can be found circulating in serum, frequently in complexes with immunoglobulin. The three antigens induce the production of equally distinct antibodies; HBSAb, HBCAb, and HBEAb respectively, in the course of non-chronic host infection (6,7).

The risk of vertical transmission of HBV infection is highest at birth and studies have shown that majority of infants born to HBSAg positive mothers are seronegative at birth but seroconvert within the first 3 months postpartum (8-11). HBSAg and HBEAg seropositivity confers the highest risk for virus transmission with 85% to 100% of their offspring becoming infected, while 70% to 90% progress to become chronic carriers. Mothers with lower risk who are HBSAg-positive but HBEAg-negative, presumably still transmit the virus to about 35% of their children in the absence of neonatal prophylaxis (12-15).

There are various laboratory techniques available for the detection of HBSAg including rapid tests, enzyme linked immuno-sorbent assay (ELISA) and nucleic acid amplification tests (NAATs). In lower-middle-income countries, including Nigeria, the rapid test kits are often widely employed for HBV screening. The comparative efficacy of ELISA and the rapid tests among the present cohort of pregnant women would provide a rationale for the use of either test in other high-risk populations.

Materials and method:

Study setting, design and population

This cross-sectional study was performed at the University College Hospital, Ibadan, Nigeria between November 2018 and February 2019. The 900-bed hospital is the first tertiary teaching healthcare facility in Nigeria and provides health care to a wide catchment of patients within the southwest region of Nigeria. One hundred and seventy-two (172) pregnant women, on their first antenatal visit were consecutively recruited into the study after obtaining their written informed consent. Administration of questionnaires was done to obtain the sociodemographic and clinical details of the participants.
Inclusion and exclusion criteria

All pregnant women visiting the hospital antenatal clinic for the first time and who gave informed consent were included into this study while those on subsequent visits together with those who declined consent/or refused sample collection were excluded.

Ethical clearance

Ethical clearance was obtained from the joint Ethical Committee of the University of Ibadan and University College Hospital, Ibadan before the commencement of the study (UI/EC/18/0264).

Specimen collection and storage

Five milliliters of blood were drawn from each patient. Plasma was separated from the blood sample after collection and immediately stored at -20 °C in the freezer for hepatitis B virus rapid and ELISA tests.

Rapid HBsAg ICT test and ELISA screening for HBsAg, HBeAg, HBeAb and HBCAb

All the samples were tested for hepatitis B surface antigen (HBsAg) using HBsAg rapid test kit (RTK) (LabACON, Hangzhou Biotech Biotech Company Limited, China). All the samples were further re-tested using enzyme-linked immunosorbent assay (ELISA) kit for HBsAg (Dia.Pro, Milan, Italy) according to the instructions of the manufacturers. ELISA kits for HBeAg, anti-HBeAb, anti-HbcAb and anti-HBsAb (Dia.Pro, Milan, Italy) were used according to the instructions of the manufacturers to determine HBeAg and antibodies to HBeAg, HbcAg and HBsAg.

The cutoff value for the HBsAg kit was determined according to the (mean negative control + mean positive control)/5. The positive and negative controls used were supplied by the manufacturer. Optical density (OD) was measured by an EMax Plus microplate reader (Molecular Devices), and the results were expressed as the cutoff index (COI). The COI was defined as the mean optical density difference between reactive control and non-reactive control 1.0 (RC-NRC=1.0). HBsAg detection was considered positive for a COI value ≥1. The performance of the kits was evaluated in terms of sensitivity, specificity, and overall agreement with the 95% confidence intervals (95% CI) according to the CLSI EP12-A guidelines (16).

Data analysis

Data were collected and entered into Excel spreadsheet and analyzed using EPI-INFO 7.2 statistical software. Association between socio-demographic and clinical features, and HBsAg status of the pregnant women was evaluated using the Chi-square statistic at 95% confidence interval, and statistical significance value of 0.05. Sensitivity, specificity, accuracy, positive and negative predictive values were calculated using the formulae below;

\[
\text{Sensitivity} = \frac{\text{True positive}}{(\text{True positive} + \text{False negative})} \times 100
\]

\[
\text{Specificity} = \frac{\text{True negative}}{(\text{True negative} + \text{False positive})} \times 100
\]

\[
\text{Accuracy} = \frac{(\text{True positive} + \text{True negative})}{(\text{True positive} + \text{True negative} + \text{False positive} + \text{False negative})} \times 100
\]

Positive predictive value = \[
\frac{(\text{True positive})}{(\text{True positive} + \text{False positive})} \times 100
\]

Negative predictive value = \[
\frac{(\text{True negative})}{(\text{True negative} + \text{False negative})} \times 100
\]

Results:

A total of 172 pregnant women participated in this study with 44.2% below the age of 30 years while 55.8% were ≥30 years of age. One hundred and sixty-nine (98.3%) were married and three (1.7%) were single. Majority (94.2%) had post secondary school education while the highest educational qualification for others (5.8%) was secondary school certificate examination (SSCE). Majority (87.8%) of the participants were employed while 12.2% were unemployed. Primigravid women constituted a third of the study participants (33.1%) while the other two-thirds were multigravida women (Table 1).

The prevalence rate of HBsAg among pregnant women in this study was 10.5% by ELISA test (18/172). The distribution of HBV infection (HBsAg positive) varied according to the socio-demographic characteristics as shown in Table 1. Pregnant women below the age of 30 years (11.8%) had higher prevalence rate compared to those aged above 30 years (9.4%) but the difference in the rates was not statistically significant \((p=0.560)\). All the HBsAg positive cases were among the married pregnant women. Educational level and HBV infection had a significant relationship \((X^2=4.324; p=0.038)\) with those with secondary education having a higher prevalence of 30% compared to 9.3% in those with post secondary education. The unemployed (14.3%) and those pregnant for the first time (12.3%) had a higher rate of HBV infection compared to the employed and multiparous participants respectively although there were no statistically significant differences in the rates \((p>0.05)\).

There was observed a significant relationship between HBV infection and previous HBV results \((X^2=15.259; p=0.000)\) as well as HBV infection with previous history of sexually transmitted infections (STIs) \((X^2=6.545; p=\)
Meanwhile, there was no statistically significant association between HBV infection and other correlates such as history of HBV vaccination, previous HBV screening, scarification as a child and as an adult, history of contact with HBV patient, history of surgical and dental procedure, circumcision as an adult and HIV status (Table 2).

The total number of HBsAg positive samples using the rapid test kits was 17 (9.9%) while the ELISA method identified 18 (10.5%) positive samples. Five of the 17 ELISA HBsAg positive samples tested negative with the rapid kits while 4 of the 17 RTK positive samples tested negative with the ELISA test as shown in Table 3. The calculated sensitivity was 72.2%, specificity 97.4%, accuracy 94.8%, positive predictive value (PPV) 76.5% and the negative predictive value (NPV) was 96.8%.

All the 154 HBsAg ELISA negative samples were further tested for other HBV serological markers. Thirty-seven (24.0%) tested positive to anti-Hbc only, 3 (1.9%) tested positive to anti-HBe only, 11 (7.1%) tested positive to both anti-Hbc and anti-HBe. None was positive to HBeAg and HBsAb (Table 4).

Table 1: Frequency of HBsAg distribution with respect to socio-demographic characteristics of pregnant women attending University College Hospital, Ibadan, Nigeria

| Variables                | Groups              | No tested (%) | HBsAg | X²   | p-value |
|--------------------------|---------------------|---------------|-------|------|---------|
|                         | (n=172)             |               | Positive (%) | Negative (%) |       |         |
| Age (years)              | <30                 | 76 (44.2)     | 9 (11.8) | 67 (88.2) | 0.276 | 0.560   |
|                         | 30 and above        | 96 (55.8)     | 9 (9.4)  | 87 (90.6) |        |         |
| Marital status           | Single              | 3 (1.7)       | 0 (0)   | 3 (100)  | 0.357 | 0.550   |
|                         | Married             | 169 (98.3)    | 18 (10.7) | 151 (89.3) |       |         |
| Educational level        | Secondary           | 10 (5.8)      | 3 (30.0) | 7 (70.0)  | 4.324 | 0.038*  |
|                         | Post-secondary      | 162 (94.2)    | 15 (9.3) | 147 (89.7) |       |         |
| Occupation               | Employed            | 151 (87.8)    | 15 (9.9) | 136 (89.1) | 0.373 | 0.542   |
|                         | Unemployed           | 21 (12.2)     | 3 (14.3) | 18 (85.7) |        |         |
| Parity                   | Primigravid         | 57 (33.1)     | 7 (12.3) | 50 (87.7) | 0.230 | 0.584   |
|                         | Multigravid         | 115 (66.9)    | 11 (9.6) | 104 (89.4) |       |         |

*p-value <0.05 - Statistical significance

Table 2: Frequency of HBsAg distribution with respect to clinical characteristics of pregnant women attending University College Hospital, Ibadan, Nigeria

| Variables                | Groups              | Total tested (n=172) | HBsAg | X²   | p-value |
|--------------------------|---------------------|----------------------|-------|------|---------|
|                         |                     |                      | Positive (%) | Negative (%) |       |         |
| History of vaccination   | Yes                 | 29                   | 3      | 26   | 0.036  | 0.850  |
|                         | No                  | 141                  | 13     | 128  |        |         |
|                         | Not sure            | 3                    | 2      | 1    |        |         |
| Previous HBV screening   | Yes                 | 44                   | 4      | 40   | 0.010  | 0.921  |
|                         | No                  | 125                  | 12     | 113  |        |         |
|                         | Not sure            | 4                    | 2      | 2    |        |         |
| Previous HBV result      | Positive            | 4                    | 2      | 2    | 15.259 | 0.000* |
|                         | Negative            | 47                   | 1      | 46   |        |         |
|                         | Not sure            | 122                  | 15     | 107  |        |         |
| Scarification as child   | Yes                 | 53                   | 7      | 46   | 0.615  | 0.433  |
|                         | No                  | 119                  | 11     | 108  |        |         |
| Scarification as an adult| Yes                 | 49                   | 8      | 41   | 2.512  | 0.113  |
|                         | No                  | 123                  | 10     | 113  |        |         |
| History of contact with HBV patient | Yes | 13 | 3 | 10 | 2.387 | 0.122 |
|                         | No                  | 159                  | 15     | 144  |        |         |
| History of STI           | Yes                 | 8                    | 3      | 5    | 6.545  | 0.011* |
|                         | No                  | 164                  | 15     | 149  |        |         |
| History of surgical and dental procedure | Yes | 56 | 4 | 52 | 0.978 | 0.323 |
|                         | No                  | 116                  | 14     | 102  |        |         |
| Circumcision as an adult | Yes                 | 49                   | 7      | 42   | 1.491  | 0.222  |
|                         | No                  | 123                  | 10     | 113  |        |         |
| HIV status               | Positive            | 6                    | 1      | 5    | 0.255  | 0.613  |
|                         | Negative            | 166                  | 17     | 149  |        |         |

*p-value <0.05 - Statistical significance
Table 3: Comparative efficacy of Rapid Test Kits and ELISA in HBsAg screening

| Rapid kits | ELISA | Total | Sensitivity (%) | Specificity (%) | Accuracy (%) | PPV (%) | NPV (%) | $X^2$ | p-value |
|------------|-------|-------|-----------------|-----------------|--------------|---------|---------|------|---------|
| Positive   | 13 (72.2) | 17 (9.9) | 72.2 | 97.4 | 94.8 | 76.5 | 96.8 | 87.71 | 0.00* |
| Negative   | 5 (27.8) | 155 (90.1) | 97.4 | 94.8 | 76.5 | 96.8 | 87.71 | 0.00* |
| Total      | 18 (100) | 172 (100) | 97.4 | 94.8 | 76.5 | 96.8 | 87.71 | 0.00* |

PPV – Positive Predictive Value, NPV – Negative Predictive Value; *P-value <0.05 - Statistical significance

Table 4: Presence of other HBV markers among HBsAg negative study participants

| Profile | Other HBV markers | Frequency (%) | Virological explanation |
|---------|------------------|---------------|-------------------------|
| A1      | Anti-HBc only    | 37 (24.0)     | Resolved or occult HBV infection |
| A2      | Anti-HBe only    | 3 (1.9)       | Resolving HBV infection |
| A3      | Anti-HBc and anti-HBe | 11 (7.1) | Resolving HBV infection |
| A4      | No additional marker | 103 (66.9) | HBV infection susceptible |
| Total   |                  | 154 (100)     |                         |

Discussion:

To achieve the vision of the Global Health Sector Strategy (GHSS) to end HBV infection by 2030, accurate detection of HBV infection is very important (17). This is of greater importance among pregnant women who carry the potential risk of vertical transmission. The seroprevalence of HBsAg among pregnant women reported in this study was 10.5%. The finding from the current study is similar to the reports from a 13-year meta-analytical study which documented 11.5% HBsAg seroprevalence (18). Similar observations among a cohort of pregnant women have also reported HBsAg seroprevalence range of 5.4-12% (19-22). A study among pregnant women from Mali has also reported a seroprevalence of 10.5% (23), while 9.2% was observed in Gambia (24) and 17.3% in Burkina Faso (25). Contrastingly lower levels have been reported from other parts of Africa including; 2.4% in Rwanda, 4.9% in Uganda (26) and 5.6% in Sudan (7).

The level of endemicity of HBV infection in these regions contribute to the prevalence rate observed among the cohort studied. Several studies among other populations within Nigeria have reported HBsAg prevalence ranges that vary between 5 and 18% (28-30). All these studies affirm the hyper-endemicity status of Nigeria and underscore the need for an efficient screening method for HBV infection particularly among pregnant women. The lower HBsAg seroprevalence rate of 2% reported from Western Europe and United States of America might be due to increased access to vaccination services for HBV as well as better infection prevention and control practices towards hepatitis B prevention (31).

The sensitivity of the rapid test used in this study was 72.2% with an accuracy of 94.8% compared with ELISA. This is lower than 90% sensitivity and 99.9% accuracy reported in Bangladesh (32). Previous authors have also reported higher sensitivity for rapid test kits; 97% (33) and 93.4% (34) from two different studies in India. A lower sensitivity of 51.6% sensitivity was reported in South East, Nigeria (35). The rapid test kits are widely used for screening for hepatitis B infection in Nigeria hence the need to assess their efficacy particularly among important risk groups. A false negative HBsAg result among pregnant women pre-empts the need for administration of prophylactic hepatitis B immunoglobulin post-delivery. This increases the risk of development of chronic liver disease among in adulthood (36,37). Although, ELISA offers a more reliable option for the detection of HBsAg, the feasibility of its routine utilization for screening purposes is reduced because of its higher cost, requirement for additional equipment as well as a longer turn-around-time.

There was no significant association between HBV infection and socio-demographic
characteristics such as age, marital status, parity and occupation. There was however a significant association with level of education of the participants ($\chi^2=4.324; p=0.038$); those with secondary education had a higher prevalence rate compared with those with post-secondary education. Donbraye et al., (20) reported a similar observation with 59.3% HBsAg seroprevalence rate among those with only secondary education. This suggests that education informs risk taking behavior that might impart on hepatitis B virus infectivity. This is however different from the report of Opaley et al., (38) where the more educated pregnant women had a higher rate of HBsAg prevalence, thus suggesting possibility of other confounding factors.

Previous positive HBV results and past history of other sexually transmitted infections (STIs) were significantly associated with HBsAg seropositivity. Previous history of STI suggests possible co-infection with HBV due to similarity in mode of transmission. Earlier studies reported similar association as observed in the current study (39,40). Other possible risk factors for HBV infection such as history of HBV vaccination, previous HBV screening, scarification as a child and as an adult, history of contact with HBV patient, history of surgical and dental procedure, circumcision as an adult and HIV status were not significantly associated with HBsAg seropositivity among the pregnant women, which is similar to earlier reports among the same study population (39-41). This finding however contrasts report by Rukunuzzaman and Afroza (43) in their study among a different study population.

Thirty-seven (24%) of the HBsAg negative pregnant women were positive for anti-HBc only, while 3 (1.9%) had anti-HBe only, and 11 (7.1%) had both anti-HBc and anti-HBe. The 24% anti-HBc in this study is far higher than previous findings among pregnant women in other reports; 1.5% reported by Zahn et al., (44) among pregnant women, 5.4% by Adetunji et al., (45) among apparently healthy individuals and 17% by Oluyinka et al., (46) among blood donors in Ile-Ife. HBsAg negative pregnant women with anti-HBc often have low hepatitis B viral load but remain potentially infectious (47-49). The detection of anti-HBe in some pregnant women in this study signifies the resolution of the HBV infection while seropositivity to both anti-HBc and anti-HBe markers connotes convalescent stage.

All the HBsAg seronegative pregnant women also tested negative for HBeAg and HBsAb thus confirming that although none of them was in the active replication phase of HBV infection but all were susceptible to hepatitis B infection. This finding is not surprising as majority of the participants were unvaccinated against hepatitis B virus.

**Conclusion:**

Although the HBsAg seropositivity is high among the study population, the efficacy of rapid test kits compared to ELISA is low. ELISA is recommended for HBV screening among pregnant women to prevent false-negative results. There is need to develop a safer antenatal screening strategy for HBV possibly by combining the use of the less sensitive rapid screening techniques with the more sensitive ELISA method to limit vertical transmission of hepatitis B virus. The high number of unvaccinated HBV-susceptible pregnant women justifies the need for increased advocacy for HBV vaccination.

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