

Chronic Hepatitis B Virus Infection and Rubella Susceptibility Among Obstetric Population in Metropolis Antenatal Centre Kano, Nigeria

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Abstract

It is well known that hepatitis B virus (HBV) infection is endemic in Nigeria. However, increased rubella susceptibility has been shown in patients from the Asian pacific region where chronic HBV infection is endemic. This study was carried out to assess the relationship between chronic HBV infection and rubella susceptibility in obstetric population aged 15–47 years attending Antenatal Clinic at Muhammad Abdullahi Wase Specialist Hospital Kano, Nigeria. From a total of 288 patients screened, 31 (10.76%) were reactive for HBsAg, meanwhile 50 (17.36%) were reactive to rubella IgM. Among the 31 infected patients 15 (48.39%) were from 20 – 24 years age bracket representing the most susceptible age group while the infection rate was lowest (0.35%) in 45 – 49 age group (P = 0.00). The results of serological markers shows that HBsAg (+) was found in all 31 subjects

(100%), anti HBs (+) 0 (0.00%), HBeAg (+) 3 (9.68%); anti HBe (+) and anti HBc (+) 24 (77.42%) respectively ($P = 0.09$). The study of liver enzymes activity among the HBV positive patients shows abnormal Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) among HBsAg (+) and HBeAg (+) group. However, abnormal Alkaline phosphatase (ALP) was found to be non-significantly different between HBsAg (+) and HBeAg (+) vs HBsAg (+) and HBeAg (-) groups ($P=0.00$). Moreover, obstetric histories such as abortion still birth and neonatal deaths among various age groups with respect to rubella was also studied, it implies that out of the 50 reactive patients, 35(12.15%) had a previous abnormal obstetric history ($P=0.02$). In a comparative study conducted, it was observed that HBV carriers were (25.81%) susceptible to rubella as against (12.91%) observed in HBV free subjects (positive correlation). The study demonstrates strong associations between chronic HBV infection and rubella susceptibility among the studied population.

Keywords: Chronic; Hepatitis B virus; Infection; Obstetrics; Rubella; Sero-markers; Susceptibility.

1. Introduction

Early detection of infections such as Human immunodeficiency virus (HIV), hepatitis B, syphilis and rubella in pregnancy can lead to health gains for both mother and child [1,2]. Effective treatment and intervention can be offered to prevent onward transmission of HIV and hepatitis B [3,4] and reduce the risk of congenital infectious diseases [2].

Hepatitis B virus (HBV) is a DNA virus causing hepatitis in humans. It accounts for 400 million chronic infections worldwide [5] and is hyperendemic in sub-Saharan Africa and Asia [6,7]. It is thought to be the main etiological factor in over 75% of chronic liver diseases [7]. Transmission of HBV results from exposure to infected blood or body fluids, unprotected sexual contact, blood transfusion, the use of contaminated needles and syringes, and vertical transmission (from mother to child) [8]. The risk of Peri-natal infection among infants born to HBeAg-negative mothers ranges from 10% to 40%, with 40%-70% of these infected remain chronically infected [9]. Children born to HBsAg-positive mothers who do not become infected during the Peri-natal period remain at a high risk of infection during early childhood. HBV-related liver diseases or hepatocellular carcinoma (HCC) are responsible for over a million deaths per year and represent 5-10% cases of liver transplantation [10,11]. HCC is one of the most common cancers worldwide, HBV being responsible for at least 75% occurrences [9].

Testing for HBV infection in pregnancy has been of importance in respect of morbidity and mortality of the host (pregnant women), likewise its effect on the process of parturition, and the risk of vertical transmission [12]. The contaminated new-born most often remains a chronic carrier with the consequences of liver cirrhosis, and HCC. Mother-to-child transmission can be avoided by vaccination of the newborn [12]. This intervention to stop vertical transmission can only be applied when the status of the pregnant woman is known.

Rubella, commonly known as German measles is a disease caused by the rubella virus. The name "rubella" is derived from the Latin, meaning little red. It is generally a mild illness and serious complications are rare. However, primary maternal rubella virus infection during the first trimester of pregnancy carries a high risk for

the development of congenital rubella syndrome (CRS) with characteristic malformations of the heart, eye and ear or even death of the fetus. As of December 2012, a total of 132 (68%) WHO member states had introduced rubella-containing vaccine (RCV), a 33% increase from 99 member states in 2000. A total of 94,030 rubella cases were reported to WHO in 2012 from 174 member states, an 86% decrease from the 670,894 cases reported in 2000 from 102 member states [13]. In Nigeria, previous studies on pregnant women revealed rubella IgG prevalence of 68.50% in Ibadan [14], 54.10% in Maiduguri [15] and 76.00% in Lagos [16]. In western Nigeria, [17] showed that an average of 68.00% of the Nigerian population possessed rubella antibody [18]. Therefore on the average, 66.20% of pregnant women in Nigeria are already immune to rubella infection probably due to subclinical or clinical exposure to the virus as there is no policy for immunization against it and there is a 33.80% susceptible population [18]. To prevent prenatal HBV infection and future cases of CRS, the advisory committee on immunization practices, the American Academy of pediatrics (AAP) and American college of obstetrics and Gynecology recommended routine prenatal screening to identify women who carry the hepatitis B surface antigen (HBsAg) and rubella IgG and post-partum vaccination of women who lack evidence of rubella immunity [19,20,55].

2. Materials and Methods

2.1. Study area

The investigation was carried out at antenatal clinic, Muhammad Abdullahi Wase Specialist Hospital Kano. It is one of the reference hospitals in the state where people from various parts of the state and neighboring states of various backgrounds attend.

2.2 Study Population

A total of 288 pregnant women of homogenous sex and of different age groups, ethnicities, educational and socio-economic status, who filled the consent forms were recruited for this study using standard epidemiological formula. Thirty one control samples were used for comparison based on HBsAg sero-positive cases.

2.3 Study Design

A descriptive study was used to design a cross-sectional (prevalence) survey which was carried out according to the ethical standard for human experimentation. An ethical clearance was obtained from Hospitals Management Board Kano State.

2.4 Limitations

Some obstacles such as time frame, short of funding and compliance were encountered along the course of the research

2.5 Virological Examinations

2.5.1 Screening for Hepatitis B surface Antigen (HBsAg)

All the samples were tested for Hepatitis B surface antigen (HBsAg) using rapid chromatographic immunoassay for the qualitative detection of HBsAg. The test strips and sera were allowed to equilibrate to room temperature (25-30⁰C) prior to testing.

- **Procedure**

The test strip contains anti HBsAg particles and anti – HBsAg coated on the membrane. The tape from the test card was peeled off and the test strip was stocked in the middle of test card with arrows pointing down on the test card. The dropper was held vertically and 3 drops of the serum (75µL) was transferred onto the “specimen pad” of the test strip. A drop of buffer (40µL) was added and the appearance of the colored line(s) was observed within 15 minutes [21].

2.5.2 Test for Serological Markers

The one step cassette style HBV test (combo) is rapid test based on the principle of immunoassay combined colloid gold technology. The HBV test is a diagnostic device to detect the 5 markers (HBsAg, HBeAg, anti-HBe, anti-HBc and anti-HBs) associated with Hepatitis B virus infection.

- **Procedure**

The test kit was removed from the pouch and placed horizontally on a desk. Three drops of the serum sample was added into each well marked 1-5 and three drops of buffer was also added in each well. The results were read after 15 minutes [21].

2.6 Biochemical Analysis

2.6.1 Alanine Amino Transferase (ALT)

- **Procedure**

About 0.1ml of serum sample was placed in one tube (tube 1); another 0.1ml of standard solution was also added into a separate tube (tube 2). 0.5ml of phosphate buffer solution (R1) was then added to

both tube 1 and 2. Five milliliter (5.0ml) of 2, 4 – dinitrophenyl hydrazine solution (R2) was also added to both tube 1 and 2. The preparation was mixed and incubated for 30 minutes at 30⁰C. 5.0ml of sodium hydroxide (NaOH) was added and incubated for exactly 20 minutes at 25⁰C. Another 5.0ml of (NaOH) was added to both tubes. The preparation was mixed and read spectrophotometrically at 546nm wavelength [22].

2.6.2 Aspartate Amino transferase (AST)

- **Procedure**

About 0.1ml of serum sample was placed in one tube (tube 1); another 0.1ml of standard solution was added into a separate tube (tube 2). 0.5ml of phosphate buffer solution (R1) was then added to both tube 1 and 2. Then 5.0ml of 2, 4 – dinitrophenyl hydrazine solution (R2) was added into the tubes. The preparation was mixed and incubated at 30°C for 30 minutes. Then 5.0ml of sodium hydroxide (NaOH) was added and incubated at 25°C for 20 minutes. Another 5.0ml of (NaOH) was added to both the tubes. The preparation was mixed and read spectrophotometrically at 546nm wavelength [22]

2.6.3 Alkaline Phosphatase (ALP)

- **Procedure**

About 0.5ml of alkaline phosphate reagent was placed in a tube labeled T and another 0.5ml in another tube labeled B. 50µl of serum sample was added to tube T, while 50µl of reagent blank was also added to tube B. The preparation was mixed and incubated at 37°C for 10 minutes. 2.5ml of alkaline phosphatase color developer was added to both the tubes and read spectrophotometrically at 590nm [22].

2.6.4 Screening for Rubella Antibody (Rubella IgM)

Rubella virus antibody was analyzed using enzyme-linked immunosorbent assay (ELISA) which is the most sensitive and reliable procedure for detection of antibodies to Rubella [23].

- **Procedure**

Each serum sample was diluted 1:40 with serum diluent and placed in the 93 microwells of the microtitre plate and then incubated at room temperature for 30 minutes. About 100µl of negative control, low positive and high positive standards were added in separate microwells. The preparation was washed three times and another 100µl of enzyme conjugate was dispensed into each well and incubated at room temperature for 30 minutes. This was then washed three times again and followed by the addition of 100µl Tetramethylbenzidine (TMB substrate) into each well and incubated at room temperature for 30mins. The reaction was stopped by the addition of 100µl of stop solution. The test was repeated 4 times. The color intensity of the solution in each well was measured using a microwell reader with a 450 nm filter [24].

3. Results

From the 288 sera samples screened, 31 were sero – reactive for HBsAg while 50 were reactive to rubella IgM antibody and 2 were sero – reactive to HIV. The overall prevalence for HBsAg was found to be (10.76%), of the 31 HVB sero-positive subjects, 15 (5.22%) were from the 20 – 24 years age bracket representing the most susceptible age group while the sero-positivity rate decline in 35 – 39, 40 – 44 and 45 – 49 years age groups respectively (Table 3.1).

Table 3.1: Summary of Overall Virological Assay

Age group (years)	Serological Testing n = 288				Serological Markers n = 31					
	No screen ed	HBsAg reactive (rapid screening)	HIV reactive (rapid screening)	Rubella IgM reactive (ELISA)%	NO. Screened	HBsAg(+)	AntiHBs(+)	HBeAg(+)	AntiHBe(+)	AntiHBc(+)
15 – 19	12	2 (0.70)	0 (0.00)	2(9.52)	2 (0.70)	2(0.70)	0(0.00)	1(3.23)	2(6.45)	2(6.45)
20 – 24	115	15(5.22)	0 (0.00)	20(17.40)	15(5.22)	15(5.22)	0(0.00)	2(6.45)	12(38.71)	10(32.26)
25 – 29	81	7(2.44)	0(0.00)	15(18.52)	7(2.44)	7(2.44)	0(0.00)	0(0.00)	5(16.13)	7(22.58)
30 – 34	45	5(1.74)	2(0.70)	7(15.56)	5(1.74)	5(1.74)	0(0.00)	0(0.00)	3(9.68)	2(6.45)
35 – 39	22	1 (0.35)	0(0.00)	5(22.73)	1(0.35)	1(0.35)	0(0.00)	0(0.00)	1(3.22)	2(6.45)
40 – 44	3	0(0.00)	1(0.35)	1(33.33)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
45 – 49	1	1(0.35)	0(0.00)	0 (0.00)	1(0.35)	1(0.35)	0(0.00)	0(0.00)	1(3.22)	1(3.22)
Total (%)	288	31(10.76)	2(0.70)	50(17.36)	31(10.76)	31(10.76)	0(0.00)	3(9.68)	24(77.42)	24(77.42)

Key:

HBsAg: Hepatitis B surface antigen; **Anti HBs:** antibody to Hepatitis B surface antigen; **HBeAg:** h\Hepatitis Be antigen; **Anti HBe:** antibody to HBeAg; **Anti – HBc:** antibody to \Hepatitis B core antigen.

Table 3.2 determines liver enzymes activity among the HBsAg sero-positive subjects. Abnormal ALT and AST test were elevated in serum samples of subjects with HBsAg (+), and HBeAg (+) groups. However, the abnormalities in ALP were found to be non-significantly different between HBsAg (+) and HBeAg (+) VS HBsAg (+) and HBeAg (-) groups. The rate of abnormal ALT (70.97%) was higher than that of abnormal AST (58.06) and abnormal ALP (32.30) in HBsAg (+) subjects (P = 0.00).

Table 3.3 indicates Sero-prevalence of Rubella IgM Antibodies among Chronic HVB carriers in relation to Obstetric Losses with ages. Obstetric histories among various age groups with respect to rubella IgM sero – prevalence was observed. Of the 50 sero – reactive rubella IgM studied, 35 had previous abnormal obstetric histories. Abortions had the highest percentage 22(62.86%) with highest prevalence (2.39%) among 30 – 34 years age group and least (1) (2.86%) in 15 – 19 and 40-44 years age groups.

Premature delivery was observed to be almost uniform across all the ages, but with 11.40 % prevalence rate. Still birth was found to have the same prevalence rate with that of premature delivery but with the highest prevalence among 20 – 24 age groups (2.86%). However, congenital anomalies, was found to have the least prevalence rate of 5.70%. However, neonatal death had the prevalence rate of 8.60% with decline frequency towards the ages of 35 – 49 years (P = 0.02).

The comparison of rubella susceptibility with chronic HBV carriers and free subjects (non-carriers) was shown in Table 3.4. Rubella susceptibility was found to be 25.81% among the HBV sero-positive subjects as against 12.91% of HVB free subjects (P=0.03).

Table 3.2: Determination of the Liver Enzymes Activity among HBsAg Sero-positive Subjects n = 31

Mode	Number Screened	LiverEnzymes		
		Abnormal ALT n (%)	Abnormal AST n (%)	Abnormal ALP n (%)
HBsAg (+)	31(100)	22 (70.97)	18 (58.06)	10 (32.25)
HBsAg (+) and HBeAg (+)	3(9.68)	3 (9.68)	2 (6.45)	1 (3.23)
HBsAg(+) and HBeAg (-)	28(90.32)	12 (38.71)	8 (25.81)	2 (6.45)
Normal values		0 to 12 u/L	0 to 12 u/L	9 – 22 u/L

Key: *ALT:* Alanine aminotransferase
AST: Aspartate Aminotransfearse
ALP: Alkanine Phosphate

Table 3.3: Sero-prevalence of Rubella IgM Antibodies among Chronic HVB carriers in relation to Obstetric Losses with ages

	No. of IgM Seropositivity of Rubella Among Various Age Group (Years)							Total (%)
	15 – 19	20 – 24	25 – 29	30 – 34	35 – 39	40 – 44	45 – 49	
Obstetric history								
Abortions	1(2.86%)	3(8.57%)	5(14.29%)	8(22.84%)	4(11.42%)	1(2.86%)	0(0.00%)	22 (62.90)
Premature delivery	0(0.00%)	1(2.86%)	0(0.00%)	1(2.86%)	1(2.86%)	0(0.00%)	0(0.00%)	4 (11.40)
Still birth	0(0.00%)	2(5.71%)	1(2.86%)	0(0.00%)	1(2.86%)	0(0.00%)	0(0.00%)	4 (11.40)
Congenital anomalies	0(0.00%)	1(2.86%)	0(0.00%)	1(2.86%)	0(0.00%)	1(2.86%)	0(0.00%)	2 (5.70)
Neonatal death	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)	1(2.86%)	1(2.86%)	3 (8.60)
Total (%)	1(2.86)	7(20.00)	6(17.14)	10(28.57)	7(20.00)	3(8.57)	1(2.86)	35 (100)

= 0.02)

Table 3.4: Comparison of Rubella Susceptibility with HBV Carriers and HBV Free Subjects

Age group (years)	Chronic HBV Carriers		Control	
	HBV-Carriers (%)	Rubella Susceptibility (%)	HBV non Carriers (%)	Rubella Susceptibility (%)
15 – 19	2 (6.45)	0(0.00)	2 (6.46)	0(0.00)
20 – 24	15 (48.38)	5 (16.13)	15 (48.38)	2 (6.45)
25 – 29	7 (22.58)	2 (6.45)	7 (22.58)	1 (3.23)
30 – 34	5 (16.13)	1 (3.23)	5 (16.13)	1 (3.23)
35 – 39	1 (3.23)	0(0.00)	1 (3.23)	0(0.00)
40 – 44	0 (0.00)	0(0.00)	0 (0.00)	0(0.00)
45 – 49	1 (3.23)	0(0.00)	1 (3.23)	0(0.00)
Total (%)	31 (100)	8 (25.81)	31 (100)	4 (12.91)

4. Discussions

It is well known that HBV infection is endemic in Nigeria. Even though studies have been carried out on hepatitis B virus infection in different parts of the country, and different sub – groups of individuals, information regarding its prevalence in pregnant subjects is scanty especially from the north – eastern region [9].

The classification of high endemicity for HBV infection has been defined as HBsAg greater than 7.00% in adult population [25]. The HBsAg sero-positivity of 10.76% among pregnant women in our study (Table 3.1) shows that the North-eastern region as in other parts of Nigeria was found to be endemic for HBV infection. The result of this study is in conformity with an earlier finding that sub-Saharan Africa has HBV carrier rate ranging from 9.00% to 12.00% [26]. The sero-prevalence rate of 10.76% for HBV infection in this study is higher than the 2.90% found in pregnant women in Port Harcourt, South – South Nigeria by [27] 9.60% in Anambra [28], 8.90% in Ibadan [29], 8.30% in Zaria [30], 8.20% in Ilorin [9] and 6.08% in Lagos [31]. It is also higher than the 6.2% found women in Sierra Leone [32], the 2.50% found by [33] in pregnant Iranian women and the 1.53% found by [34] amongst pregnant women attending government maternity hospitals in Kabul.

The figure 10.76% from this study was however found to be lower than the 11.00% found by [35] among the pregnant women in Makurdi, North – Central Nigeria. It was found to be lower than 11.60% found by [36], 12.30% in Minna [37], 12.50% in Enugu [38] and the 12.60% found by [39] among pregnant women in Maiduguri, North eastern part of the country, and a rural community in North Central region respectively. It is also lower than the 13.80% found by [40] in pregnant Senegalese women in Dakar and equally lower than the 63.30% found by [41] in Jos, North – Central Nigeria. The variation in the sero-prevalence may be due to geographical variation and differences in cultural practices.

Most of the previous studies did not distinguish between recent and past infections; screening for HBsAg alone does not fully reflect epidemiology of the disease as it could not indicate a carrier state, viral replication, or chronic stage; this study differentiated carriers of HBsAg from those with active infection. The assay for serological markers of HBV infection such as anti-HBs, HBe, anti-HBe and anti-HBc was carried out. These antigens and their homologous antibodies are considered to be specific markers of the HBV infection [42]. The result obtained shows that all the HBV sero-positive samples were also confirmed by the appearance of double band in HBsAg hole of the HBV combo test kit. HBsAg was the first to appear after exposure to HBV. Three samples (9.68%) were reactive to HBeAg which indicate that there was active viral replication or soluble antigen present in the circulation (Table 3.1). Young adult (30-35 years) have been reported to have high rates of HBeAg – positivity (28.57%), and the rate of positivity decreased with age and this is in line with the finding of [43] which could be due to spontaneous sero – conversion to the antibody against HBeAg. Older carriers have been shown to be more likely than younger carriers to clear [43]

Antibody to HBe appeared to be reactive by (77.42%) (Table 3.1); 24 out of 31 subjects were reactive to anti HBe. Presence of anti HBe in serum of HBsAg carrier suggests lower titer of HBV and also to antibody to HBc; (77.42) of the samples was equally reactive. This indicates infections with HBV of some undefined time in the past, and also it is an indication that the infection was resolved. All the sero-positive HBsAg were non-reactive to antibody to HBsAg which signifies that none of the subject acquire the infection as a result of vaccination and none of the subject was fully protected as affirmed by [42,44].

The association between the serological markers in HBV sero-positive subjects was measured statistically and found significant ($P < 0.05$). A high prevalence of HBV infection was found with 20 - 24 years age group (5.22%) followed by the 25 – 29 (2.44%) then 30 – 34 years age group (1.74%) (Table 3.1), this prevalence is in line with the finding of [9]. This may be because age range of 20 – 34 is the most sexually active and more fertile.

The sero-prevalence rate of 17.36% was reported for rubella in this study (Table 3.1); the subjects studied had detectable IgM level which is a marker of recent infection. Detection of IgM was well established as a means of diagnosing recent CRS and was recommended by the WHO as the primary test for the laboratory confirmation of rubella which is in concordance with the study of [45] with 17.50% prevalence rate and that of [46] with 17.70% prevalence rate. However, the figure 17.36% is in line with the WHO Worldwide prevalence rate of rubella susceptibility (7.5 – 17.40%) [47]. The result obtained was found to be higher than 4.20% found in pregnant women in Makurdi Benue State [18] and 10.00% also among pregnant women attending antenatal clinic Benin Teaching Hospitals [48]. Moreover, [49] and [50], reported 6.50% and 10.38% respectively. Whereas [51] has reported rubella IgM positivity to be 26.80%. The difference in the prevalence rates may be due to the seasons in which the samples were collected, geographical location, cultural behavior, ethnicity, sexual behavior and socio-economic status. The wide variation may also be due to the fact that the study area was visited by different group of people from various destinations of multiple ethnicities.

The study of liver enzymes between various groups with chronic HBV infection showed that the increased liver enzymes level were significantly higher in HBsAg (+) (70.97%) when compared with normal values (Table

3.2). Moreover, subject positive for both HBsAg and HBeAg were more likely to have abnormal values of liver enzymes compared with HBsAg carriers negative for HBeAg. Thus, measurement of aminotransferase levels remains the most common and convenient way to identify liver inflammation in patients with chronic HBV infection. But the relationship may be better established by serial observation and analysis rather than by simple examination of aminotransferase levels as shown by [52]. Liver enzymes were found to have positive correlation with HBV sero-positivity which is in conformity with the finding of [56,53].

All the women that participated in this study were between the ages of 15 – 47 years. Although the highest prevalence was observed in 20 – 24 years age (Table 3.3), statistical analysis indicates that there is no significant difference between them (rubella has no relationship with age groups) as $P > 0.05$. This agree with the finding of serologic survey rubella IgM in pregnant in Makurdi which shows that ($P > 0.05$) and considered statistically not significant [18]

In comparative study conducted at the tip of the research. It was observed that HBV chronic carriers are more susceptible to rubella virus infection, (25.81%) of hepatitis B chronic subjects were reactive to rubella IgM antibody as against (12.91 %) (Table 3.4). This may be due to the fact that in chronic HBV infection, HBsAg and HBeAg or HBsAg and anti HBe persist at elevated levels for at least six months or up to life time in some individuals [42]. Chronic carriers of HBsAg may or may not have demonstrable evidence of liver disease. Persistent (unresolved) viral hepatitis, a mild benign disease that may follow acute hepatitis B in 8 – 10% of adult patients, is characterized by sporadically abnormal aminotransferase values and hepatomegaly. Fulminant HBV disease is associated with super infection with some other agents [44].The association between chronic HBV and rubella susceptibility was measured and found to be statistically significant ($P=0.03$). This shows that there is strong association between chronic HBV and rubella susceptibility. Although a major section of pregnant women in Nigeria are immune, the finding of the study shows that cases of rubella infection still occur in Nigeria among pregnant women which is in conformity with the finding of [54]. This dispels the notion among many hospital workers who think that rubella is no longer an issue. Nigeria has in its hand opportunity to eliminate this virus since the burden is low and the actual susceptible population is small and elimination of rubella and CRS is National Public Health Goal [21].

5. Conclusion

The finding of this study confirms that HBV is endemic among pregnant women attending antenatal clinic, Muhammad Abdullahi Wase Specialist Hospital, Kano. The study also demonstrates associations between chronic HBV infection and rubella susceptibility among the studied population. Moreover, most people of the region are not aware of the aforesaid disease hence vertical transmission is very much possible to occur.

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