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Maternal determinants of intrauterine transmission of HBV in West Africa: A prospective study

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ABSTRACT

In sub Saharan Africa, chronic infection with hepatitis B virus (HBV) still represents a significant burden of disease and death. In Ivory Coast, despite the introduction of anti-hepatitis B vaccine in the extended program of immunization of the WHO, toddlers and children remain a segment of the population frequently infected with HBV. The conditions of early HBV transmission, and notably the materno-fetal route, have been studied in details in Eastern Asia but remain barely documented in sub Saharan Africa. We analyzed the socio-demographical and viral features explaining HBV transmission in 163 HBsAg(+) expectant mothers and their 169 newborns. Statistical analyses were performed using a Prism 8.1.2 statistical package. We observed that mothers significantly at risk to transmit either HBV DNA to their babies were presenting HBV DNA loads>5.0 log10 IU/mL (P=1.1 E-13). These mothers, who represent around one third of the series (34.3%, n=56/163) were younger than non-transmitting ones (25.5±5.8 years vs 28.2±5.8 years, P=0.0187) and displayed a slightly lower rate of successful pregnancies (parity/gravidity, 0.24±0.29 vs 0.36±0.33, P=0.025). Remarkably, the fates of newborns either positive for HBsAg or HBV DNA who completed immune-prophylaxis were drastically different at 9-12 months. While a majority (90%, n=18/20) of HBsAg(+)-only babies became anti-HBs(+), 62.5% (n=5/8) DNA-positive newborns failed to mount a proper anti-HBs response (OR=15.0, 95%CI=2.1-89.1, P=0.0095). In general, 10.7% (n=3/28) of newborns with at least one positive HBV marker at birth developed a *bona fide* chronic infection at 9 months. In Ivory Coast, pregnant women presenting HBV DNA loads above 5.0Log10 IU/mL are at risk of maternofetal transmission. The presence of HBV DNA in the blood of newborns represents a better predictor of anti-HBV immunization failure than HBsAg presence. An adaptation of immunization procedures with a passive immunoprophylaxis targeting newborns at risk should be urgently considered.

Key words: HBV, sub-Saharan Africa, viral loads, materno-fetal transmission, genotype E.

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INTRODUCTION

Persistent infection with the hepatitis B virus (HBV) still represents a very significant burden of severe pathologies and deaths in Sub-Saharan Africa and the Western part of this continent remains more affected than any other African sub-regions (Ott et al., 2012). Reasons explaining precisely this situation are barely documented but could be plausibly linked either to a high historical endemicity of HBV in the region, to a greater infectivity of the local HBV genotype (genotype E), or to the precarious hygiene conditions that prevails in a group of countries overall characterized by a lower human development index than in the rest of Africa and by a low level of health expenditure *per capita*

(Mulders et al., 2004; Tognarelli et al., 2015; Petti et al., 2006; Govender, 2005).

Regarding HBV transmission, it is commonly transmitted by exposure to contaminated blood products, by sexual intercourse, by poorly defined horizontal transmission through casual familial contacts or in the perinatal period, due to pre-delivery micro-transfusions and at delivery by contamination in the genital tract of the mothers (Kwon and Lee, 2011). The moment of lifespan at which transmission occurs is paramount as it conditions the capacity of the virus to install a persistent infection. It is considered that early infection with HBV, that is, *in utero*, at birth (pseudo-vertical transmission), or during the first 4 to 5 years of life, is at risk to become lifetime persistent in 70-90% of cases (Ranger-Rogez and Denis, 2014). This situation is presumably due to the immaturity of children's immune system and to the intrinsically immune tolerant nature of the liver that has to accommodate the massive pro-inflammatory signals received during the establishment of the gut microflora in the first weeks of lifespan (Tiegs and Lohse, 2010; Torow and Hornef, 2017). For West African countries, it is, thus, a strategic aim for Public Health to break early life transmission of the virus, as young chronic carriers represent a renewed HBV reservoir that will sustain high local endemic levels (Thio et al., 2015). Furthermore, and despite a usually mild disease, young patients are generally more infectious than older ones due to the commonly higher viral replication and corresponding DNA loads in their bloodstream (Sokal et al., 2013).

In sub-Saharan Africa, the role played by vertical *sensu stricto* or perinatal transmission of HBV is still a matter of debate with authors considering that it is a major route of transmission while, for others, intra-household transmission through casual contacts between toddlers and infected members of the family is, in reality, preponderant (Martinson et al., 1998; Lohouès-Kouacou et al., 1999). The role played by the vertical or perinatal transmission of HBV has been studied in great detail in Eastern Asia. It came to the conclusions that *in utero,* infections are infrequent but that natural delivery represents a significant risk of infection when HBV DNA loads of the mother are high (>5.3log10 IU/ml). In such circumstances, the treatment of mothers with an antiviral is recommended. In the 24 h following birth, administration to the newborn of anti-hepatitis B immunoglobulins (100IU) and of a dose of anti-hepatitis B vaccine will provide efficient protection against perinatal and subsequent HBV transmission risks (Hou et al., 2019. This procedure suffers, however, from a certain proportion of failure that occurs essentially when a heavy HBV DNA burden affects the expectant mother and overflows preventative measures.

In West Africa, surveys on perinatal HBV transmission are scarce (Olaleye et al., 2013). Due to the limitation of available resources, it is nevertheless still necessary to better define who among pregnant women is at risk to transmit the virus in order to make them and their babies benefit from the most appropriate prophylactic treatment. With the aim to better characterize clinical and biological determinants of perinatal HBV transmission in West Africa, we analyzed a series of 163 pregnant women seropositive for HBV surface antigen (HBsAg) and their 169 babies.

PATIENTS AND METHODS

Patients

A series of 163 Pregnant women were prospectively recruited in the Gynecology, Gastroenterology, and Neonatalogy departments of the Cocody University Hospital and at the Institut Pasteur of Côte d'Ivoire from June to November 2018. All pregnant women were positive for HBsAg and attended care at the prenatal consultation in the Gynecology department. None of the mothers received antiviral therapy during pregnancy. All expectant mothers gave their written informed consent to participate in the study. The 163 mothers gave birth to 169 newborns as there were six twin pregnancies. This study was approved by the National Committee for Ethics and Research (CNER) and complied with the rules of the Helsinki Convention.
Blood sampling of mothers took place before delivery. Newborn's blood samples were collected before receiving the first dose of the anti-hepatitis B vaccine.

Serological and virological analyses

The blood samples were centrifuged to collect 250 to 500 µl of sera and/or plasma which were stored at -80°C before further analyzes. Markers of infection with HBV (HBsAg, total anti-HBc) were investigated in neonates using Cobas® 6000 (Roche) and Architect plus i1000sr (Abbott). Viral loads were determined in mothers using the Roche CAPCTM automaton. Viral DNA was extracted from plasma using an Invitrogen kit according to the manufacturer's recommendations. The DNA extracts were eluted in tubes and stored at -20°C before PCR analysis with the GenAmp PCR System 9700 (Applied Biosystems, USA) using a 25 µl reaction mixture.
A nested PCR was carried out to amplify and genotype HBV strains. This method uses an in-house primer pair for outer PCR and the method of Farazmandfar *et al*. for the inner PCR and genotype determination steps.The primers are listed in Table 5 (Farazmandfar et al., 2012).

Statistical analyses

All statistical analyses were performed using a Prism 8.1.2 statistical package (San Diego, CA). Numerical variables were summarized by their median, mean and range

Table 1: Demographical features of HBsAg(+) mothers.

Demographical features of expectant mothers	
Age (Years, mean±SD)	27.4±4.9
Education (%)	
No schooling	20.8 (34/163)
Primary school	19.6 (32/163)
Secondary school	44.2 (72/163)
University	14.7 (24/163)
Professions (%)	
Housewives	34.3 (56/163)
Shopkeepers	29.4 (48/163)
Hairdressers	9.2 (15/163)
Students	7.9 (13/163)
Needlewomen	5.5 (9/163)
Accountants	3.0 (5/163)
Teachers	1.8 (3/163)
Secretaries	1.8 (3/163)
Miscellanous	6.7 (11/163)
Citizenship (%)	
Ivorian	80.3 (131/163)
Burkinabe	7.9 (13/163)
Malian	3.6 (6/163)
Beninese	0.6 (1/163)
Guinean	1.2 (2/163)
Nigerian	3.6 (6/163)
Nigerien	2.4 (4/163)
Languages (%)	
Afro-asian	3.6 (6/163)
Akan	33.1 (54/163)
Gur	19.6 (32/163)
Kru	9.2 (15/163)
Mandé	28.8 (47/163)
Yoruba	3.6 (6/163)
Miscellanous	1.8 (3/163)
Familial situation (%)	
Singles	20.8 (32/163)
Cohabitants	55.8 (91/163)
Married	23.3 (38/163)

according to their distribution types. Comparisons were made either with a Student T-test or a Mann-Whitney test as appropriate. Categorical variables were summarized as frequencies that were compared using Fischer exact test. All tests were two-sided and the level of significance was set at $p<0.05$.

RESULTS

The mean age of the 163 expectant mothers was 27.4±4.9 years. The demographical characteristics of participants are shown in Table 1. In summary, a minor subset of them did not benefit from any schooling (20.8%). Occupations of the mothers were primarily housewives (34.3%) and shopkeepers (29.4%). A large majority was Ivorian (>80%) and the more represented ethnolinguistic groups were Akan (33.1%) and Mandé (28.8%) distantly followed by Gur languages-speaking women (19.6%). The most prevalent risk of infections was excision (27.6%) followed by the sharing of different categories of objects (weaving and toiletries, 17.7%, Table 2). Taken together, all iatrogenic risks (surgery, transfusion, dental care, cesarean section) reached 20.0% of cases. No notion of familial hepatitis was recovered among participants.

The mean child number per mother was 1.3±1.6 before the delivery that motivates inclusion in the current study (Table 3). The mean pregnancy length was 38.0±2.7 weeks. All women were HBsAg carriers but infection with HIV was infrequent (4.9%). More than 90.0% of mothers were

Table 2: Risk factors in HBsAg(+) mothers.

Infectious risk factors	% (n)
Excision	27.6 (45/163)
Weaving instruments sharing	9.8 (16/163)
Toiletries sharing	7.9 (13/163)
Surgical antecedents	8.5 (14/163)
Scarification	6.1 (10/163)
Dental treatment	6.1 (10/163)
Cesarean section	5.5 (9/163)
Blood transfusion	1.2 (2/163)
Jaundice antecedents	0.6 (1/163)
Homosexuality	0.0 (0/163)
IV Drug use	0.0 (0/163)
Tatooes	0.0 (0/163)

Table 3: Biological features of HBsAg(+) mothers.

Clinical features of Expectant mothers	
Gravidity (mean±SD)	2.8±1.8
Parity (mean±SD)	1.3±1.6
Pregnancy length (weeks, mean±SD)	38.0±2.7
Blood Groups (%, n)	
A	25.3 (38/150)
B	23.3 (35/150)
AB	9.3 (14/150)
O	42.0 (63/163)
Rhesus	94.6 (142/150)
Serologies (%, n)	
HBsAg(+)	100.0 (163/163)
anti-HBc(+)	100.0 (163/163)
anti-HIV(+)	4.9 (8/163)
anti-Rubella virus	91.3 (137/150)
anti-*Toxoplasma gondii*	20.0 (30/150)
anti-*Treponema pallidum*	0.0 (0/150)
HBsAg quantification (Log10 IU/mL, mean±SD)	3.5±0.9
HBV DNA (Log10 IU/mL, mean±SD)	4.5±1.3

carrying anti-Rubivirus IgG while only 20.0% were immune-reactive to *Toxoplasma*. Mean and median HBV surface antigen levels were 3.5±0.9 log10 IU/mL and 3.6 log10 IU/mL (Inter-quartile range, IQR=2.8-4.2) respectively. The corresponding values for HBV DNA were 4.5±1.3 Log10 IU/mL and 4.2 Log10/mL (IQR=3.7-5.1). All deliveries occurred through natural routes.

Regarding the viral features observed in newborns, 21.2% were seropositive for HBsAg (n=35/165) whereas 10.3% (n=17/165) presenting detectable HBV DNA in their plasma could be scored as intrauterine infections (Table 4). Three newborns (1.8%) were presenting both markers. In general, 29.6% (n=49/165) of the newborns carried at least one of the two markers investigated. All HBV strains were belonging to genotype E. We decided to explore the clinical and/or biological bases explaining the passage of these markers in newborns bloodstream.

We first intend to characterize the maternal features associated with the presence of either HBsAg or HBV DNA in the plasma of newborns. No socio-demographical features or medical antecedents were associated with the early transmission of HBV biomarkers from mother to

Table 4: Clinical and biological features of newborns (n=169).

Clinical features of newborns	
Sex ratio M:F	1.3 (96:73)
Stillbirth (%, n)	2.9 (5/169)
Twins (%, n)	3.7 (6/163)
Cranial perimeter (cm, mean±SD)	32.0±2.3
Birthweight (g, mean±SD)	2944±634
Size (cm, mean±SD)	48.2±3.4
APGAR score 5' (mean±SD)	7.6±1.5
HBsAg(+) (in %)	20.7 (35/169)
anti-HBc(+) (in %)	99.4 (168/169)
HBV DNA (%)	10.0 (17/169)

Table 5: Sequences of primer pairs used for nested PCR.

Primer IDs	Séquences d'ADN (3'-5')	Positions	Polarité
MD-S	CCGCGTCGCAGAAGATCTCAATC	2417-2440	Sens
MD-R	CCGGAACTGGAGCCACCAGCAGG	56-79	Anti-sens
Common1-F (A,D,E,H)	AGTATTCCTTGGACTCATAAGGTGG	2457-2481	Sens
E1-R (E)	CTAGGGGCAAATATTTCGTAGAGA	2659-2682	Anti-sens
H1-R (H)	GTCCCATGCCCCTTCTCGC	2869-2887	Anti-sens
D1-R (D)	AGGTGTCCTTGTTGGGATTGTAA	2948-2970	Anti-sens
A1-R (A)	GGCAGGAGGAGGAATTGTTGA	3118-3138	Anti-sens

child. HBsAg sero-reactivity of newborns was not associated with any variables.

By contrast, in the case of HBV DNA detection in the plasma of the baby, various clinical and biological traits were different in the transmitting mothers and non-transmitting ones. Mothers of HBV DNA (+) newborns were four years younger (24.5±6.2 years vs 28.0±6.0 years, P=0.0267) and tended to be more often, albeit non significantly, anti-HIV (+) (17.6 vs 4.1%, OR=4.83, 95%CI=0.6792-28.1649, P=0.0604, ns). We observed that none of them was carrying anti-toxoplasma IgG (0.0% vs 25%, P=0.0223). Parameters defining HBV infection were markedly more severe in these mothers. In mothers who transmitted HBV DNA, circulating HBsAg levels were significantly higher (4.2±0.4 Log10, IU/ml vs 3.4±0.8 Log10 IU/ml, 2.2 E-05) just as were HBV DNA loads (6.5±1.4 Log10 IU/ml vs 4.3±1.0 Log10 IU/ml, 5.7 E-12). The rate of transmission was 24% for mother carrying HBV DNA loads with 5 to 6 log 10 IU/mL, while it was 50% for those above 6log10 IU/ml (see Figure 1). All mothers who transmit HBV DNA presente loads above 5.0 Log10 IU/ml (100 000 IU/ml). In general, above 5.0 log10 IU/ml, the transmission rate of HBV DNA was 30.3%.

Regarding consequences for the clinical status of the newborns, positivity for either HBsAg or HBV DNA were associated with a lower birth weight (2720±703g vs 3035±582g, P=0.003) and a slightly lower body size (47.4±3.7cm vs 48.6±3.3cm, P=0.0490).

HBV DNA loads above 5.0 log10 IU/ml were thus the most important parameter conditioning viral transmission from mothers to newborns. This subset of expectant mothers represents in our study a bit more than one-third of the series (n=56/163, 34.3%). We thus wonder whether these women differ from other participants for any of the socio-demographical, ethnolinguistic or clinical parameters. The mean age of mothers with HBV DNA>100 000 IU/ml was three years younger than other mothers (25.5±5.8years vs 28.2±5.8years, P=0.0187) (Figure 1). The number of live children for these mothers was lower than in other women (0.9±1.3 vs 1.5±1.7, P=0.0128). Interestingly, the ratio of successful pregnancies (ratio parity/gravidity) was lower for mothers of the upper median for HBV DNA loads (0.24±0.29 vs 0.36±0.33, P=0.025). Interestingly, both age (Spearman r=-0.21, P=0.0054), parity (Spearman r=-0.23, P=0.0028), and the ratio of successful pregnancies (Spearman r=-0.22, P=0.0032) were inversely correlated with HBV DNA loads. As expected, circulating HBsAg levels were significantly higher in the upper median for HBV DNA (4.3±0.3 Log10 IU/ml vs 3.6±0.7 log10 IU/ml, P=5.9 E-22). Finally, we observed that Akan ethnicity tended to be, albeit not significantly, more represented in the upper median of HBV DNA loads (42.8% vs 28.2%, P=0.0791, ns).

We next wonder whether each of the marker values (HBsAg or HBV DNA) would have a predictive value regarding the future status of the newborn concerning HBV

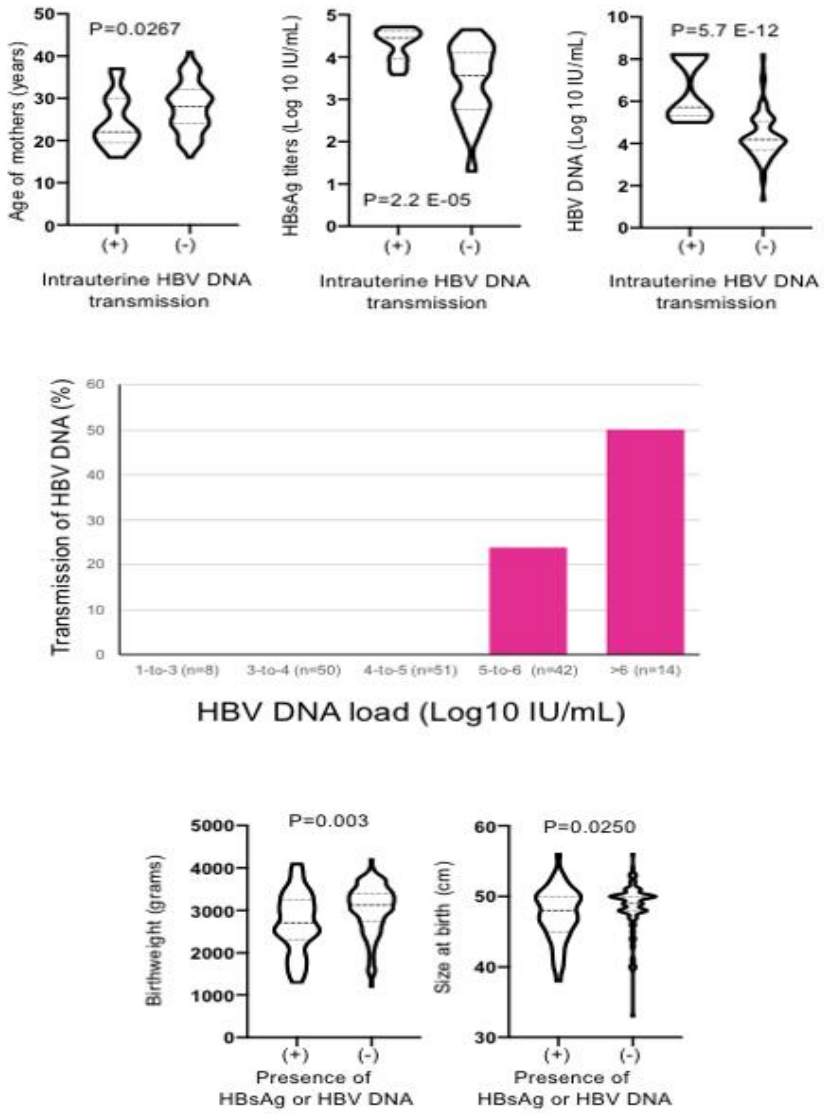

Figure 1: Intra-uterine transmission of HBV DNA according to age of mothers, AgHbs title and Birth weight.

persistence later in life (Figure 2). Out of the subset of 49 newborns presenting either marker, one died shortly after birth while 20 others were lost in follow-up. Among the 28 remaining babies brought back for consultation by their parents between 9 and 12 months, 20 were only seropositive for HBsAg, 7 were positive for HBV DNA and a single one was presenting both markers at birth. All of them completed immune-prophylaxis against hepatitis B. Remarkably, the fates of newborns either positive for HBsAg or HBV DNA at birth were drastically different. A majority (90%, n=18/20) of HBsAg(+)-only babies became anti-HBs(+) and 2 remained positive for HBsAg (10%). By contrast, among those presenting HBV DNA in their blood at birth, 62.5% (n=5/8) failed to mount detectable anti-HBs response with one of them affected with an overt persistent HBsAg(+) infection (n=1/8, 12.5%). Despite the small size of the series analyzed, the difference in the capability to mount a sufficient anti-HBs response according to the nature of HBV marker in blood at birth was, thus, very significant (OR=15.0, 95%CI=2.1-89.1, P=0.0095) and HBV DNA presence could be considered as a predictor of poor response to vaccination. Unfortunately, we did not have the possibility to check the response to anti-HBV vaccine in a large series of newborns without HBV DNA in plasma albeit born from mothers with HBV DNA>5.0log10 IU/ml. However, four newborns with HBsAg in plasma but no HBV DNA were born from mothers with HBV DNA>5.0log10 IU/ml. All of them (n=4/4) developed a satisfying anti-HBs response post-immunization. This observation suggests that HBV DNA presence in the plasma of newborns is a better predictor or poor response than high maternal viral loads.

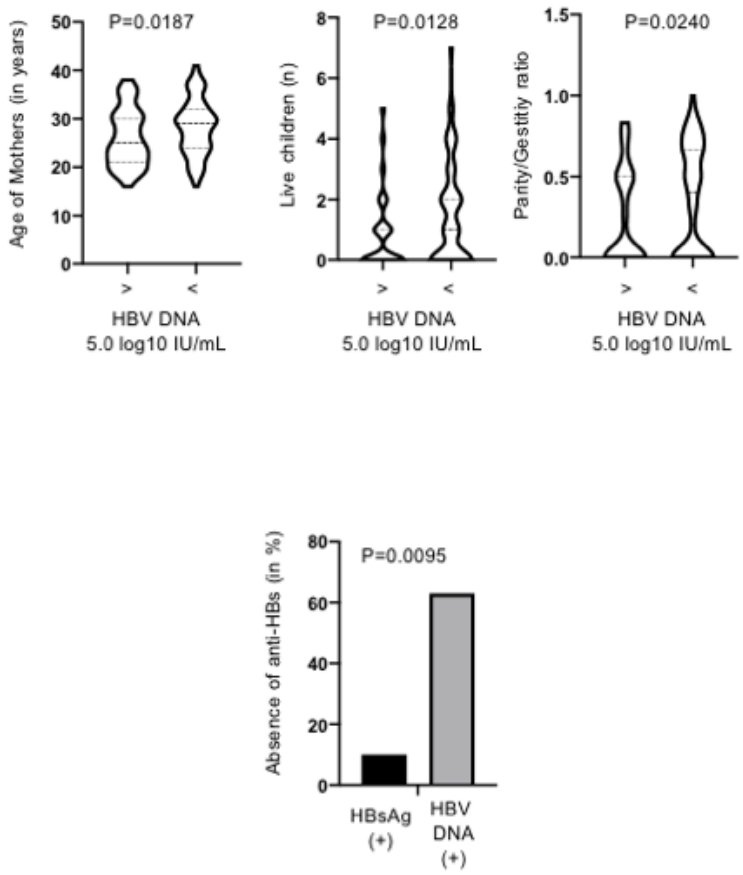

Figure 2: HBV DNA log evolution according to age of mothers, parity/gestity ratio and live children.

In general, 10.7% (n=3/28) of newborns who presented at least one HBV biomarker at birth and completed the immunization schedule, were chronically infected between 9 and 12 months).

Only genotype E of HBV have been isolated from mothers (who transmitted HBV) and their newborns.

CONCLUSION

In conclusion, a subset of Ivorian mothers with high HBV DNA loads (>5.0log10 IU/ml) are at risk of maternofetal transmission of HBV DNA. Although, this marker is not the invariable sign of a future chronic infection, it is associated with a poor response to anti-HBV immunization, and, therefore to a prolonged susceptibility to infection. In general, when measured at birth, the rate of intrauterine transmission of HBV is grossly in line with previous report from the region (Lohouès-Kouacou et al., 1999; Olaleye et al., 2013; Candotti et al., 2007). However, at 9 months of age, only 10% of infants developed a bona fide chronic infection. Further experiments are now required to determine whether or not occult B infection can be found in this population of young patients despite the administration of a complete anti-hepatitis B immunization program (Shahmoradi et al., 2012).

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