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Evaluation of liver enzymes in asymptomatic chronic hepatitis B virus infected pregnant women

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Abstract

Background The major risk factor for perinatal transmission of hepatitis B virus (HBV) infection and/or immunoprophylaxis failure is the level of maternal HBV-DNA. The aim of this study was to evaluate commonly used laboratory parameters in HBeAg-negative chronic HBV-infected pregnant women and to correlate the findings with the presence or absence of viremia.

Methods 166 consecutive chronic HBV-infected pregnant women were hematologically, serologically and virologically evaluated between the 28th and 32nd week of gestation. 101 women were finally evaluated (66 HBV-DNA positive and 35 HBV-DNA negative). Twenty-one women exhibited HBV-DNA levels above 2000 IU/mL.

Results Viremic women exhibit significantly higher ALT (25.43 IU/L vs. 15.50 IU/L, P=0.016) and GGT (17.47 IU/L vs. 10.22 IU/L, P=0.001) values as well as significantly lower white blood cell (10527 vs. 13793, P=0.008) and neutrophil count (7776 vs. 11088, P=0.001), compared to non-viremic women. The optimal cut-off points discriminating those women with a high probability to have detectable serum HBV-DNA were 7 IU/L for GGT (sensitivity = 81.6%, specificity = 69.6%, area under the ROC curve (AUC) = 75.3%) and 12 IU/L for ALT (sensitivity = 74.1%, specificity = 56.2%, AUC = 65.4%). The positive predictive value of detectable HBV-DNA in women with both serum parameters above the new limits proposed was 88.8% whereas the negative predictive value was 75%.

Conclusion Presence of HBV-DNA in maternal blood during the third trimester of pregnancy is significantly associated with maternal serum GGT levels. Women with GGT above 7 IU/L and ALT above 12 IU/L have a higher probability of HBV-DNA presence in maternal blood.

Keywords Hepatitis B, HBV-DNA, ALT, GGT, hemodilution, pregnancy

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Introduction

Vertical transmission of hepatitis B virus (HBV) infection during the perinatal period is the major cause of HBV transmission in endemic countries of the world. Of the estimated 350 million individuals chronically infected with HBV worldwide, it is generally accepted that at least 50% acquired their infections either perinatally or in early childhood, especially in countries where HBV is endemic [1]. Passive-active immunoprophylaxis failure is mainly observed in newborns from HBeAg-positive chronic HBV-infected women with high HBV-DNA levels during perinatal period [2-4]. It has been suggested that in these highly viremic women, HBV-DNA presence in cord blood as well as in placenta tissue represents a significant predictor of mother to infant HBV transmission [4].

Several recently published reports and expert opinions conclude that the major risk factor for immunoprophylaxis failure is the level of maternal HBV-DNA during the third trimester of pregnancy [5-9] and some experts in the field suggest that chronic HBV-infected pregnant women should be screened for HBV-DNA presence between week 28 and week 32 of pregnancy, in order to decide about the necessity of offering treatment with FDA class B nucleoside or nucleotide analogues in highly viremic pregnant women [5-7]. More-

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over the importance of maternal viremia has been clearly documented in recently published articles, as it is positively associated with cord blood viremia, a parameter that seems to strongly affect pregnancy outcome [10].

Pregnancy induces physiologic (palmar erythema, spider angiomas etc.) and biochemical changes (low serum albumin levels, high serum alkaline phosphatase levels etc.), often mistaken for signs of liver disease [11,12]. Serum aspartate transaminase (AST) as well as alanine transaminase (ALT) and gamma-glutamyl transpeptidase (GGT) levels remain within normal values in uncomplicated pregnancy whereas high levels of serum aminotransferases, bilirubin or uric acid during pregnancy are abnormal findings and should prompt a diagnostic workup [11,12]. Moreover due to pregnancy-induced immune-mediated changes as well as pregnancy-induced plasma volume expansion, serum aminotransferase levels seem to remain within normal values even in pregnant women with pre-existing chronic liver disease. To our knowledge there are few studies, mainly from South-Eastern Asia, in which the HBeAg-positive form of the infection and the HBV genotypes B and C are dominant in the biochemical and serological course of chronic HBV infection during pregnancy and post-partum [13]. Data from Europe which evaluates the biochemical and hematological status of HBeAg-negative chronic HBV-infected pregnant women in late pregnancy and during the postpartum period are limited [14]. Moreover there are no data concerning the maternal serum biochemical status during the third trimester of pregnancy in relation to the presence or absence of viremia among HBeAg-negative chronic HBV-infected pregnant women.

The aim of this study was to evaluate the hematological and biochemical status among a group of HBeAg-negative chronic HBV-infected pregnant women and to correlate the findings with the presence or absence of viremia.

Materials and methods

Between September 2008 and May 2011 a total of 166 chronic HBV-infected pregnant women were consecutively evaluated clinically, hematologically, biochemically and serologically between 28th and 32nd week of gestation and then gave birth at the Departments of Obstetrics and Gynecology of "Elena Venizelou" Maternal and Perinatal Hospital of Athens, Greece. A total of 2.0 mL serum was obtained from chronic HBV-infected women and four 0.5 mL aliquots from each sample were kept at minus 80˚C until measurement. Viral load in 0.5 mL sample was determined by using the Cobas TaqMan HBV Test (lower detection limit: 8 IU/mL), based on two major processes: a) manual specimen preparation to obtain HBV DNA; and b) automated PCR amplification of target DNA using HBV specific complementary primers, and detection of cleaved dual fluorescent dye-labeled oligonucleotide detection probes that permit quantitation of HBV target amplified product (amplicon) and HBV Quantitation Standard DNA. The HBV Quantitation Standard DNA, was processed, amplified, and detected simultaneously with the specimen.

Hepatitis B surface antigen (HBsAg), hepatitis B e-antigen (HBeAg), antibody to hepatitis B e-antigen (anti-HBe), antibody to hepatitis B core antigen (anti-HBc), antibody to hepatitis B surface antigen (anti-HBs), antibody to hepatitis C virus (anti-HCV), antibody to hepatitis D virus (anti-HDV) and antibodies to human immunodeficiency virus (anti-HIV) were detected using routine commercially available enzyme immunoassays (Abbott Laboratories, Abbott Park, Illinois, US). Routine hematological and biochemical tests were performed using automated techniques.

Pregnant women with the HBeAg-positive form of chronic HBV infection, women with co-infections (HCV, HDV, HIV) and women with any known pre-existing liver disease were excluded from the study. Moreover women with non-singleton pregnancy, women with known pregnancy-related complications (diabetes, hypertension, preeclampsia, placenta haemorrhage, etc.), women taking medications (except for iron, folic acid, calcium and other vitamins or diet supplements) as well as those with other known bacterial, fungal, parasitic or viral infections during pregnancy were also excluded from the final analysis.

Written informed consent was obtained from all the women of our study population. The study was performed in accordance with the 1975 Declaration of Helsinki and was reviewed and approved by the "Elena Venizelou" Hospital Ethics Committee.

Statistical analysis

Continuous variables are presented as mean values ± standard deviation. The comparison between the two subgroups of the study was made using Student's t-test, after testing for the equality of variances using Levene's test. Cut-off point analysis using the receiver operating characteristic (ROC) curves was applied to evaluate the level of ALT or GGT value by which we achieved the best predictive ability (combination of higher sensitivity and specificity) regarding detectable serum HBV-DNA. All tests were two-sided at a significance level of 0.05. Data were analyzed using STATA™ statistical software (Version 9.0, Stata Corporation, College Station, TX 77845, USA).

Results

Fifty-four women were excluded from the final analysis, according to the exclusion criteria of the study, due to: non-singleton pregnancy (n=13), diabetes of pregnancy (n=12), intrahepatic cholestasis of pregnancy (n=4), pregnancy related hypertension and/or preeclampsia (n=12), recurrent urinary tract infections (n=4), HBeAg-positive serological status (n=4) and HBV/HCV (n=2), HBV/HDV (n=2) or HBV/HIV co-infection (n=1). Among the remaining 112 pregnant women with chronic HBV infection who were finally evaluated in our study, HBV-DNA test was available in 101 women, due

to technical or serum storage problems. Sixty-six (65.3%) of them were HBV-DNA positive whereas 35 (34.7%) were HBV-DNA negative. Among 66 viremic chronic HBV-infected pregnant women, 21 (31.8% of the viremic population or 20.8% of the total population with available HBV-DNA test) exhibited HBV-DNA levels above 2000 IU/mL and 12 of them had HBV-DNA levels above 10000 IU/mL. The main laboratory parameters of the study population are presented in Table 1. As we can observe from this table the mean serum AST (31.58 IU/L) and ALT (32.70 IU/L) levels of our study population were within normal values but near the upper normal reference values of our laboratory (35 IU/L), despite the pregnancy related hemodilution as suggested by the relatively low serum albumin, creatinine and sodium levels presented. The mean serum GGT level was 13.96 IU/L, a value that could be considered very low in relation to the proposed upper normal reference values of our laboratory (52 IU/L).

In Table 2, the hematological and biochemical data of viremic and non-viremic chronic HBV-infected pregnant women are presented. We observe that viremic women exhibit significantly higher serum GGT (17.47 IU/L vs. 10.22 IU/L, P=0.001) and ALT (25.43 IU/L vs. 15.50 IU/L, P=0.016) values as well as significantly lower white blood cell (10527 vs. 13793, P=0.008) and neutrophil count (7776 vs. 11088, P=0.001), compared to non-viremic women. Despite the significant statistical difference between GGT and ALT levels among viremic and non-viremic women the mean GGT and ALT levels remain within normal limits proposed by our laboratory in both groups (even in the group of viremic chronic HBV-infected women).

Using multiple logistic regression analysis we observed that the absolute neutrophil count of pregnant women was the only predictor of viremia among HBeAg negative chronic HBV-infected women (OR=1.322, 95% CI: 1.095-1.595, P=0.004). In other words, the possibility of having undetectable HBV-DNA was increased by 32.2% for every 1000/μL increase in the absolute neutrophil count.

The optimal cut-off points discriminating those women with a high probability to have detectable serum HBV-DNA were 7 IU/L for GGT (sensitivity=81.6%, specificity = 69.6%, area under the ROC curve (AUC)=75.3%) and 12 IU/L for ALT (sensitivity=74.1%, specificity = 56.2%, AUC=65.4%), as shown in Fig. 1. It is important to note that only 4/112 (3.57%) and 19/112 (16.96%) chronic HBV-infected pregnant women of our study population exhibited abnormal serum GGT or ALT levels, respectively, according to the proposed reference values of our laboratory. The positive predictive values for the prediction of viremia in women with GGT>7 IU/L or ALT>12 IU/L were 85.1% and 75.4%, respectively whereas the corresponding negative predictive values were 64% and 54.5%, respectively. Among 36 chronic HBV-infected pregnant women with both parameters above the new proposed values (GGT>7 IU/L and ALT>12 IU/L), 32 exhibit HBV-DNA positivity and only 4 did not exhibit viremia (positive predictive value 88.8%). On the other hand, among 16 women with both parameters below the new proposed values (GGT≤7 IU/L and ALT≤12 IU/L), HBV-DNA was detected in 4 (25%) whereas the majority (12/16) of those women were not viremic (negative predictive value 75%).

Table 1 Hematological, biochemical and virological characteristics of the study population

	Mean	SD
Age (years)	27.55	6.03
Hct (%)	35.86	4.00
Hb (g/dL)	11.75	1.39
WBC (x1000)	11.595	4.284
PNL (x1000)	9.635	7.339
LYMPHO (x1000)	1.888	951
PLT (x1000)	210.646	64.986
PT (sec)	11.75	2.11
PTT (sec)	27.36	4.07
INR	0.99	0.09
FIBROGEN (mg/dL)	508	104
AST (IU/L)	31.58	50.68
ALT (IU/L)	32.70	111.66
GGT (IU/L)	13.96	21.23
ALP (IU/L)	156.9	68.03
TBIL (mg/dL)	0.69	0.56
DBIL (mg/dL)	0.24	0.35
TPROT (g/L)	6.35	0.76
ALB (g/L)	3.38	0.47
GLOB (g/L)	3.04	0.41
UREA (mg/dL)	17.56	5.74
CREAT (mg/dL)	0.55	0.18
K (mEq/L)	4.16	0.57
Na (mEq/L)	137.34	2.70
LDH (IU/L)	244.31	163.38
GLU (mg/dL)	85.18	25.76
URIC ACID (mg/dL)	4.13	1.06
HBV-DNA (IU/mL)	8969.10	39245.91

SD, standard deviation; Hct, hematocrit; Hb, hemoglobin; WBC, white blood cells; PNL, polymorphonuclear cells; LYMPHO, lymphocytes; PLT, platelets; PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio; AST, aspartate transaminase; ALT, alanine transaminase; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; TBIL, total bilirubin; DBIL, direct bilirubin; TPROT, total protein; ALB, albumin; GLOB, globulins; CREAT, creatinine; K, potassium; Na, sodium; LDH, lactate dehydrogenase; GLU, glucose

Discussion

Maternal HBV-DNA levels during the third trimester of pregnancy have been associated with perinatal transmission of HBV infection as well as with passive-active immunoprophylaxis failure [1-3,9]. Moreover, presence of HBV-DNA in cord

Table 2 Hematological and biochemical characteristics among viremic and non-viremic chronic HBV-infected pregnant women

	HBV-DNA				
	Negative		Positive		
	Mean	SD	Mean	SD	p-value
Age (years)	26.85	6.36	26.95	5.82	0.743
Hct (%)	36.31	4.24	35.83	4.21	0.541
Hb (g/dL)	11.89	1.47	11.73	1.38	0.615
WBC (x1000)	13.793	5.050	10.527	3.653	0.008*
PNL (x1000)	11.088	4.697	7.776	3.372	0.001*
LYMPHO (x1000)	1.727	0.595	2.088	1.398	0.808
PLT (x1000)	216.366	67.521	210.138	76.717	0.562
PT (sec)	11.76	1.19	12.10	3.45	0.748
PTT (sec)	27.93	5.15	27.42	3.70	0.950
INR	1.00	0.10	1.00	0.11	0.934
FIBROGEN (mg/dL)	537	99	522	91	0.515
AST (IU/L)	25.39	17.55	28.65	22.59	0.288
ALT (IU/L)	15.50	12.05	25.43	26.35	0.016*
GGT (IU/L)	10.22	13.33	17.47	29.15	0.001*
ALP (IU/L)	178.54	78.40	165.01	60.15	0.418
TBIL (mg/dL)	0.73	0.69	0.61	0.35	0.517
DBIL (mg/dL)	0.31	0.58	0.15	0.10	0.971
TPROT (g/L)	6.24	0.81	6.44	0.78	0.328
ALB (g/L)	3.29	0.49	3.40	0.53	0.487
GLOB (g/L)	2.99	0.49	3.07	0.39	0.721
UREA (mg/dL)	16.66	5.61	18.14	5.63	0.266
CREAT (mg/dL)	0.51	0.13	0.59	0.20	0.063
K (mEq/L)	4.20	0.63	4.16	0.47	0.928
Na (mEq/L)	136.53	2.94	137.53	2.49	0.268
LDH (IU/L)	229.21	70.56	271.04	231.09	0.768
GLU (mg/dL)	88.45	31.66	79.51	17.64	0.337
URIC ACID (mg/dL)	3.98	0.90	4.36	1.14	0.192

SD, standard deviation; Hct, hematocrit; Hb, hemoglobin; WBC, white blood cells; PNL, polymorphonuclear cells; LYMPHO, lymphocytes; PLT, platelets; PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio; AST, aspartate transaminase; ALT, alanine transaminase; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; TBIL, total bilirubin; DBIL, direct bilirubin; TPROT, total protein; ALB, albumin; GLOB, globulins; CREAT, creatinine; K, potassium; Na, sodium; LDH, lactate dehydrogenase; GLU, glucose

(*): significant, P<0.05

blood is significantly associated with spontaneous preterm labour in HBeAg-negative chronic HBV-infected pregnant women and women with HBV-DNA≥10.000 copies/mL during the perinatal period have a higher probability of HBV-DNA presence in their cord blood [15]. Taking into account these data it seems reasonable to evaluate all chronic HBV-infected women for HBV-DNA levels early in the third trimester of pregnancy in order to take further therapeutic decisions. On the other hand, perinatal transmission of HBV infection and/or passive-active immunoprophylaxis failure represent an extremely rare event in infants born from HBeAg-negative chronic HBV-infected mothers, even in those with detectable HBV-DNA in cord blood [15].

It seems that the relatively lower HBV-DNA levels which are generally observed in HBeAg-negative chronic HBV-infected women compared to HBeAg-positive ones as well as the absence of HBeAg expression *per se* may influence the final outcome and may protect infants from HBV infection [16,17]. Taking into consideration all these data as well as the significant cost of HBV-DNA testing we tried to find the subgroup among HBeAg-negative chronic HBV-infected pregnant women which could have the maximum possibility of detectable viremia during the third trimester of pregnancy, by evaluating commonly used laboratory parameters.

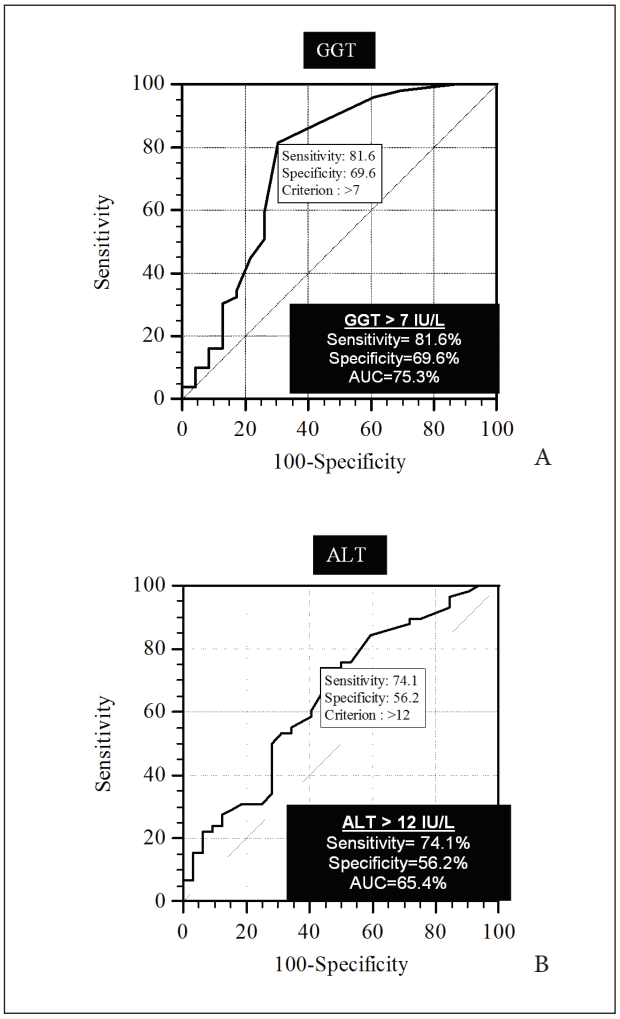

Figure 1 Receiver operating characteristic (ROC) curves evaluating the cut-off point of GGT (A) and ALT (B) level that gives the best predictive ability of having detectable HBV-DNA

In this study we found that about a third of the study population (34.1%) presented undetectable HBV-DNA levels during the third trimester of pregnancy, using a sensitive PCR assay, and more than two thirds (68.18%) of the viremic HBeAg-negative chronic HBV-infected pregnant women exhibited HBV-DNA levels below 2000 IU/mL. These findings are in accordance with previous studies in HBeAg-negative chronic HBV-infected pregnant women [15,16]. Moreover we observed that viremic pregnant women with chronic HBV infection exhibited significantly higher serum GGT and ALT values as well as significantly lower white blood cell and neutrophil count, compared to non-viremic women. Despite the significant statistical difference between GGT and ALT levels among viremic and non-viremic women the mean GGT and ALT levels of both groups of chronic HBV-infected women remain within normal limits proposed by our laboratory.

The physiologic leukocytosis of pregnancy represents a well known phenomenon, described early on by Rudolf Virchow, that has been very well documented and studied quantitatively [18]. There are also reports that present leukocytosis with marked left shift in the myeloid-neutrophilic lineage during the third trimester of normal uncomplicated pregnancy that normalized readily after delivery [19]. It has been reported that the elevated circulating levels of progesterone, especially during the late second and third trimester of pregnancy results in the increased numbers of circulating neutrophils while decreasing lymphocyte proportions, a phenomenon frequently observed in normal pregnancy [20]. Moreover, it has been reported that pregnant women exhibit lower lymphocyte counts than non-pregnant women [21]. Lymphocyte proliferation and activation is a well known phenomenon in patients with viral infections. Recent studies revealed that endogenous factors, such as regulatory T cells, immunosuppressive cytokines, and inhibitory receptors contribute to the impairment of virus-specific T cell responses in chronic HBV infection, perhaps reflecting the host's attempt to protect itself against immune-mediated pathology in a subset of patients [22]. Viremic pregnant women of our study population, exhibited significantly lower absolute numbers of white blood cells and neutrophil counts and significantly higher ALT and GGT values, compared to non-viremic women. Moreover, we observed that the absolute neutrophil count of pregnant women was the only predictor of viremia among HBeAg negative chronic HBV-infected women (the lower the absolute neutrophils count the higher the possibility of detectable viremia). It seems that the presence of viremia affects the well known pregnancy-induced leukocytosis as well as the left shift in the myeloid-neutrophilic lineage. The absolute lymphocyte count in viremic chronic HBV-infected pregnant women was higher than the corresponding count in non-viremic ones (2.088 vs. 1.727 respectively, P=0.808), although not significant, probably because of the major effect of pregnancy *per se* in the absolute neutrophil count. This finding needs further investigation in large-scale studies.

Pregnancy-induced endocrine and immune changes result in elevation of HBV-DNA levels and normalization of liver tests between the first, second and third trimester of pregnancy in chronic HBV-infected women [14]. Moreover, the well-known pregnancy-related plasma volume expansion and serum dilution [11,12], especially during the third trimester of pregnancy, might significantly affect serum HBV-DNA levels as well as serum ALT and GGT levels, so both parameters may be underestimated during late pregnancy. In our study we found significantly higher GGT and ALT levels in viremic HBeAg-negative chronic HBV-infected pregnant women compared to non-viremic women, with the mean levels of both serum liver tests being within the normal range proposed by the laboratory, even in the viremic population. We observed that GGT levels above 7 IU/L or ALT levels above 12 IU/L could predict viremia with a sensitivity of 81.6% or 74.1% and specificity of 69.6% or 56.2%, respectively. The combination of both serum parameters for the prediction of viremia among HBeAg-negative chronic HBV-infected pregnant women during the third trimester of pregnancy gives a positive predictive value of 88.8% and a negative predictive value of 75%.

Limitations of the study are the relatively small sample size of the study population and the small percentage of patients with high (>2000 IU/mL) or very high (>10.000 IU/mL) HBV-DNA levels, as usually observed in HBeAg-negative chronic HBV-infected population. Since vertical HBV transmission may still occur only in highly viremic pregnant women, the prediction of HBV DNA detectability alone has rather limited clinical relevance and therefore additional studies including pregnant women with higher viremia levels are required to evaluate the significance of the findings of this study in clinical practice. No adjustment was made for inflation of type I error due to multiple comparisons. On the other hand we believe that the study population does represent the total HBeAg-negative chronic HBV-infected population, in which a considerable proportion of inactive carriers (patients with low or undetectable HBV-DNA levels, normal ALT values and absence of significant liver disease) exist. Despite these limitations we believe that this group of HBeAg-negative chronic HBV-infected Caucasian pregnant women, evaluated with respect to maternal virological, biochemical and hematological data, and the advantages of the study, such us the use of a central laboratory where all serological and virological tests were performed using the same methods, outweigh the limitations.

In conclusion, the presence of HBV-DNA in maternal blood during the third trimester of pregnancy seems to be associated with maternal serum GGT and ALT levels in HBeAg-negative chronic HBV-infected pregnant women. Women with serum GGT levels above 7 IU/L appear to have a higher probability of HBV-DNA presence in maternal blood. A combination of GGT levels above 7 IU/L and of ALT levels >12 IU/L may offer better accuracy in the discrimination of viremic from non-viremic chronic HBV-infected women during the third trimester of pregnancy. These preliminary findings deserve to be evaluated in larger cohorts, as their confirmation might reduce the need for expensive HBV DNA testing in a significant proportion of chronic HBV-infected pregnant women.

Summary Box

What is already known:

- Vertical transmission of hepatitis B virus (HBV) infection during perinatal period is the major cause of HBV transmission in endemic countries of the world
- Passive-active immunoprophylaxis failure is mainly observed in newborns from HeAg-positive chronic HBV-infected women with high HBV-DNA levels during perinatal period
- Chronic HBV-infected pregnant women should be screened for HBV-DNA presence between week 28 and week 32 of pregnancy, in order to decide about the necessity of offering treatment/prophylaxis in highly viremic cases
- Serum aminotransferase and GGT levels seems to remain within normal values even in pregnant women with pre-existing chronic liver disease due to pregnancy-induced immune-mediated changes as well as due to pregnancy-induced plasma volume expansion

What the new findings are:

- Presence of HBV-DNA in maternal blood during the third trimester of pregnancy seems to be associated with maternal serum GGT and ALT levels in HBeAg-negative chronic HBV-infected pregnant women
- Women with serum GGT levels above 7 IU/L appear to have a higher probability of HBV-DNA presence in maternal blood
- A combination of serum GGT levels above 7 IU/L and of ALT levels above 12 IU/L may offer better accuracy in the discrimination of viremic from non-viremic chronic HBV-infected women during the third trimester of pregnancy to avoid costly HBV-DNA testing in a significant proportion of them

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