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Hepatitis B in Pregnant Females. A Cross Sectional Study in Nile Delta, Egypt

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ABSTRACT

Background & Aims: Hepatitis B infection is a worldwide health problem. Egypt classified as an area of intermediate endemicity. Hepatitis B has high materno-fetal transmission. The aim of this study was to assess hepatitis B virus infection in Egyptian pregnant females in Nile Delta as regards risk factors and magnitude of the problem.

Subjects and Methods: This cross sectional study was performed on 1948 pregnant females. Historical and sociodemographic data were collected through short simple questionnaire. They were screened for hepatitis B surface antigens. Positive ones were subjected to test hepatitis B e antigen and viral load by real time polymerase chain reaction.

Results: Thirty patients (1.54%) were hepatitis B surface antigen positive. Only two of them (6.67%) were hepatitis B e antigen positive with high viral load. Others were hepatitis B e antigen negative and low viral load. Family history of hepatitis B, occupation, age more than 27 years, and history of surgical or dental procedures were significant risk factors associated with hepatitis B acquisition.

Conclusion: Screening for hepatitis B is important as a part of antenatal care mainly in the presence of risk factors to follow up mother, and protect fetus so as to prevent wide spread of hepatitis B in Egypt.

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KEYWORDS

Hepatitis B, Hepatitis B surface antigen, hepatitis B e antigen

List of Abbreviations

HBV = Hepatitis B virus

HBsAg = hepatitis B surface antigen

HBeAg = hepatitis B e antigen

HBcAb = hepatitis B core antibody

Introduction

Hepatitis B virus infection (HBV) is a serious infection, and is considered within the most fatal ten health problems [1, 2]. It is one of the silent killers because many people are not aware that they have HBV infection [3]. About Two billion people have history of HBV infection whatever chronic carriers, or previous infection. Acute hepatitis B can lead to fulminating hepatitis. Chronic HBV causes 700000 deaths yearly because it can be complicated with hepatocellular carcinoma even without cirrhosis, liver cirrhosis, and liver failure [4]. Hepatitis B surface antigen (HBsAg) is the main marker to detect the presence of infection; also, it helps in screening and studying the prevalence of the virus in specific

area or specific group of people [5]. In Egypt, HBV is considered intermediately endemic in 2010, with prevalence between 3 to 11% mainly in males [6].

Hepatitis B virus can be transmitted perinatally. Pregnant women infected with hepatitis B can transmit the infection to their new born during pregnancy or delivery [7]. This is associated with little knowledge about hepatitis B and absence of HBV screening in antenatal care units [8]. The risk of mother to infant transmission can reach up to 51% in Egypt [9]. The presence of active hepatitis, positive HBeAg, or high viral replication increases the risk of materno-fetal transmission [10]. However, giving the newborn a dose of hepatitis B immunoglobulin (HBVIG) and the first dose of vaccine on the first day of birth will decrease the risk that infant will have HBV infection to 10% [11]. In addition, HBV can cause maternal mortality mainly in developing countries [12]. In Egypt, routine HBV vaccination was started in 1992 on 2, 4, and 6 months of age. However, routine HBV screening in pregnant women did not take place [13]. These factors encourage the importance of addition of HBV screening using HBsAg to antenatal care program [14]. This study aimed to assess hepatitis B virus infection in Egyptian pregnant females in Nile Delta as regards risk factors and magnitude of the problem.

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Patients and Methods

Study Design, Study Site and Population

This was a cross sectional study performed between September 2019 to September 2020. Pregnant females came asking for antenatal follow up in Tanta University Hospital within this period were included in the study.

Data Collection and Processing

Approval of Ethical Committee Faculty of Medicine, Tanta University had been obtained before beginning the study. The research was explained to the participants who accepted enrollment in it, and they signed on informed consent.

Participants were asked to answer short questionnaire (as shown in Table 1) consisted of historical data, sociodemographic data, history of HBV vaccination, and history of exposure to one or more risk factor for HBV acquisition.

Table 1: Questionnaire of the Participants

Number
Age (years)
Mobile N.
Adress
Work
Gravidity status (Primi or multigravida)
Gestational age (weeks)
Hepatitis B vaccination
Family history of hepatitis B
Previous blood transfusion
History of IV drug& syringe use
History of major operations
Medical clinic or emergency unit attendance or hospital admission
History of endoscopic procedures
History of dental procedures
History of Shistosomiasis
Tattooing

Screening for HBV infection was done for all participants by HBsAg using ELISA (Murex HBsAg Version 3, Diasorin, Italy). Females who were HBsAg positive were subjected to other investigations including HBeAg and HBV DNA viral load. HBeAg was detected using (ETI-EBK PLUS, Diasorin, Italy). HBVDNA viral load was detected by real-time polymerase chain reaction (PCR). HBV-DNA was quantified by real-time detection polymerase chain reaction primers. The detection limit was 20 IU/ml.

Statistical Analysis

Statistical analysis was done using SPSS (version 22.0, IBM, New York, USA). Descriptive analysis of data was expressed in the form of number and percentage. Categorical data were analyzed using Chi-square test with Yate's (continuity). Fisher, s Exact test was used if one or more expected value <5. The set point of alpha level was 5% with significance level 95%, and a beta error accepted up

to 20% with a 80% power of study [15]. Univariate and multivariate analysis using binary logistic regression were done to evaluate the significance of risk factors for HBV infection.

Results

Demographic Criteria of the Patients

This study was performed on 1948 pregnant females. Their age ranged between 18-46 years, with mean age (27.93+5.75). There were 1519 (78%) from rural areas, and 429 (22%) from urban areas. Primigravida cases were 455 (29%), and multi gravid cases were 1463 (71%). HBsAg positivity was detected in 30 (1.54%) of them. There were directed to follow up in units of viral hepatitis and to perform full investigations. On performing of HBeAg and HBVDNA, only two cases were HBeAg positive with high HBVDNA >200000 IU/ml (Immunotolerant phase), and they were advised to come to take treatment in first trimester to prevent fetal transmission. Other cases were HBV carriers with HBeAg negative and were advised to make follow up every six months.

As in Table 2, comparison of questionnaire elements between HBV cases and others showed a significant difference in age ($p = 0.042$), family history of HBV ($p < 0.001$), history of HBV vaccination ($p = 0.045$), working in health care fields ($p = 0.046$), and history of dental procedures ($p = 0.042$). However, other data (history of blood transfusion, surgery, endoscopy, gravidity status, residence, and tattooing) did not differ significantly between both groups of the study.

Risk factors of HBV infection were analyzed using univariate and multivariate logistic regression. This analysis detected that the most significant risk factors associated with HBsAg positivity were health care field occupation ($p = 0.014$), family history ($p < 0.001$), and history of dental procedures ($p < 0.001$) (Table 3).

Table 2: Comparison between HbsAg Positive and Negative Subjects

Group	HBsAg negative (n=1918)	HBsAg positive (n=30)	P – value
Age (years) <27	967	9	0.042*
>27	951	21	
Residence Urban	421	8	0.69
Rural	1497	22	
Gravidity status Primi	446	9	0.516
Multi	1472	21	
Gestational age (weeks) (mean+ SD)	33.087+9.25	35.467+6.55	t=1.69 p=0.059
Occupation (helth care)#	2	1	0.046*
Family History of HBV	53	9	<0.001*
HBV vaccination	961	9	0.045*
Blood transfusion#	246	4	0.789
History of IV drug or syringe use#	67	2	0.288
Surgical operations	911	20	0.057

Medical clinic or emergency unit attendance#	323	4	0.806
Endoscopic procedures#	26	1	0.344
Dental procedures	319	25	<0.001*
History of Shistosomiasis#	5	0	1.000
Tattooing#	30	1	0.384

*Significant #Chi-square test with Yates correction. Other P values: Fisher's Exact Test

Table 3: Univariate and Multivariate Analysis of Hepatitis B Risk Factors

Univariate analysis			
Factor	Odds ratio	Confidence interval (95%)	P – value
Age (years) >27	2.373	1.081-5.207	0.031*
Multigravida	0.707	0.321-1.555	0.388
Occupation (health care)	33.034	2.913-374.599	0.005*
Family History of HBV	15.081	6.594-34.489	<0.001*
No HBV vaccination	2.343	1.068-5.142	0.034*
Blood transfusion	1.046	0.362-3.022	0.934
History of IV drug or syringe use	1.973	0.461-8.456	0.36
Surgical operations	2.211	1.029-4.748	0.042*
Medical clinic or emergency unit attendance	0.76	0.263-2.192	0.611
Endoscopic procedures	2.509	0.329-19.119	0.375
Tattooing	2.17	0.286-16.455	0.454
Dental procedures	25.063	9.523-65.96	<0.001*

*Significant

Discussion

Egypt is considered by World Health Organization (WHO) as intermediate area as regards epidemiology of HBV [16]. Between 1980 and 2007, studies detected that HBV prevalence in Egypt was 6.7% generally, 11.7% in Upper Egypt, 4.6 in Lower Egypt, and 4% in pregnant women [17]. In a cross sectional study performed in 2015, 1.4% of general Egyptian populations were positive for HBV with 1.9% prevalence in males, and 1.1% prevalence in females [18].

Our study showed that HBsAg prevalence was 1.54 % in pregnant women. In Egypt, many studies were made to identify prevalence of hepatitis B in different states. Similar study in 2016-2017 in Alexandria showed that HBsAg prevalence in pregnant females was 3.39% [19]. However, sample size in each study and different

socioeconomic status could result in some variability in results of studies in different Egyptian states and differences throughout the countries. In Ismailia, 18.3% of women were HbCAb positive, and 5% were HBsAg positive [20]. HBsAg seropositivity was found to be 1.56% in Benha in agreement with our study [21]. In Upper Egypt, sero-prevalence of HBsAg was 4.8% in Assiut [22]. Findings of the present study were similar to findings in Libya and Algeria. Both had low prevalence rates (1.5% and 1.6%) respectively [23]. However, Differences were detected in Saudi Arabia (4.1 %) [24], Pakistan (4.6 %) [25], Sudanese antenatal clinics (10.2%) [26], and Nepal (17%) [27]. This study showed that rural areas had HBV cases more than urban areas but the difference was not statistically significant. However; in another study in Minya, rural areas were significantly higher in prevalence than urban areas, which could be explained by different educational level, and presence of home delivery in rural areas [28]. As regards age, HBV was more prevalent in those > 27 years with significant statistical difference. However, no significant difference detected as regards gestational age in the present study. Similar findings were reported in Ethiopia, Saudi Arabia [29, 30]. Yohanes et al; agreed with our study that gestational age was not significantly related to hepatitis B infection [31]. However; in Alexandria, no significant association was detected between age or gestational age and HBV [19].

In our study, multigravidae and primigravidae did not differ significantly. This was in agreement with previous study made in Benha [21], and in Nigeria [32]. However, Azhar et al; stated that multigravidae had higher percentage of infection because of multigravidae exposure to many risk factors as multiple pregnancies, blood transfusion, and hospital admission [33]. Occupation is a risk factor for HBV infection. People who work as physician or medical staff have chance to catch the infection many times than general population [34]. Our study showed that working in health care fields was a significant risk factor for HBV acquisition. This was in agreement with Eke et al; who reported that about 25% of health care workers were HBsAg positive [35]. However, results of studies made by Taseer et al; and Sharifi-Mood et al; were not significant as regards the occupation [25, 36]. Our study also detected significant prevalence of HBsAg positivity in those with family history of HBV. This might be due to presence of contaminated infected surfaces with HBV in living areas of chronic infected ones. This was in agreement with other studies also [11].

Although blood transfusion is a risk factor for hepatitis B transmission, it was not that in this study and other studies in Egypt, Mexico, and Saudi Arabia [11, 37, and 38]. This could be due to application of screening of blood donors. However; in other countries, blood transfusion was an important risk factor [25]. In our study many cases of HBV did not take vaccine before (p=0.045). Many Egyptian studies had similar findings because many pregnant women were born before of the introduction of vaccine [33, 35]. There were some risk factors which were not significantly associated with HBV prevalence in this study (IV drug or syringe use, hospital admission, history of endoscopic procedures, history of Shistosomiasis, and tattooing), and these findings were in agreement of some studies and in disagreement with others. Taseer et al; reported the association between hepatitis B infection and multiple injection therapy [25]; also, addiction of patient's husband was found to be a significant

risk factor in another study [21]. Previous studies reported non significant difference between HBsAg positive and negative ones as regards history of hospital admission [11, 39]. However, many other studies found the significant role of hospitalization in presence of HBV infection [40].

Our study detected a significant association between HBsAg positivity and history of surgery and as well as history of dental procedures. Another study was similar to our study in which 80% of HBsAg positive cases were set for surgeries [11]. However, previous surgery was not significant risk factor in some other studies [19, 21]. Also, other studies detected that dental procedures were no longer significant risk factor for HBV. This might be attributed that large number of patients in our sample underwent dental procedures [11, 24]. Our study detected that 2 (6.67%) of 30 cases were immunotolerant with HBeAg positive and high viral load. They needed follow up and introduction of therapy in the last trimester to prevent fetal acquisition. The remaining 28 cases were carriers with HBeAg negative and low viral load. This percentage was similar to an Egyptian study made by Elsabaawy et al; in 2020. This study detected (82.4%) HBeAg negative and 33(17.6%) HBeAg positive [41]. However; in studies in Ismailia and Benha, all cases were HBeAg negative and HBeAb positive [20, 21]. Reduction of HBeAg positivity in HBV infected ones in Egypt might be attributed to improve vaccination coverage [42].

A Saudi Arabian study estimated that prevalence of HBeAg positivity was < 5%. [43]. HBeAg was negative in more than 98% and 96% of cases in Iran and Oman respectively [44, 45]. Similar pattern of prevalence of HBeAg negativity was detected in France, Greece, Italy, Portugal, and Spain [46-51].

Conclusion

Hepatitis B virus is still present in Egypt. Screening for hepatitis B in antenatal care unit is important mainly in presence of risk factors (occupation, family history, surgical, or dental procedures) for follow up and treatment of pregnant mother when treatment indicated and for protection of the fetus to prevent widespread of hepatitis B.

References

- [1] Blachier M, Leleu H, Peck-Radosavljevic M, Valla DC, Roudot-Thoraval F. The burden of liver disease in Europe: a review of available epidemiological data. *Journal of Hepatology*. 2013; 58: 593-608.
- [2] Afzali H, Heravi MM, Moravveji SA, Poorrahnama M. Prevalence of hepatitis B surface antigen in pregnant women in Beheshti Hospital of Kashan, Isfahan. *Iranian Red Crescent Medical Journal*. 2015; 17: 20596-20598.
- [3] Pungpapong S, Kim WR, Poterucha JJ. Natural history of hepatitis B virus infection: an update for clinicians. *Mayo Clinic Proceedings*. 2007; 82: 967-975.
- [4] Centers for Disease Control and Prevention. *Viral Hepatitis*. 2018. Retrieved from: <https://www.cdc.gov/hepatitis/abc/index.htm>.
- [5] Shepard CW, Simard EP, Finelli L, Fiore AE, Bell BP. Hepatitis B virus infection: epidemiology and vaccination. *Epidemiol. Rev.* 2006; 28: 112-115.
- [6] Ragheb MM. Prevalence of hepatitis B virus in Egypt: Current status in an Afro-Asian country. *Hepatology Research*. 2010; 40: 732.
- [7] Vu Lam NC, Gotsch PB, Langan RC. Caring for pregnant women and newborns with hepatitis B or C. *American Family Physician*. 2010; 82: 1225-1229.
- [8] Al-Essa, M, Alyahya A, Al Mulhim A, Alyousof A, Al-mulhim M, Essa A. Perception of and attitude towards hepatitis B infection among Saudi pregnant females attending antenatal care unit in Al-Ahsa City, Kingdom of Saudi Arabia. *Cureus*. 2020; 12: e6673.
- [9] Badawy HA, El-Salahy E. Materno-fetal transmission of hepatitis B infection. *J. Egypt Public Health Assoc.* 2000; 75: 357-367.
- [10] Chowdhury SD, Eapen CE. Perinatal transmission of hepatitis B. *Hepatitis B Annual*. 2009; 6: 80-88.
- [11] EL-Shabrawi M, Mohamed M, Hamdi, Ehab M, Khamiss S, El Karaksy H. Prevalence of hepatitis B virus infection among Egyptian pregnant women - a single center study. *International Journal of Tropical Diseases and Health*. 2013; 3: 157-168.
- [12] Tse KY, Ho LF, Lao T. The impact of maternal HBsAg carrier status on pregnancy outcomes: a case study. *J. Hepatol*. 2005; 43: 771-775.
- [13] Mansour E, Abdul-Rahim S, Batouty G, Zaghoul I, Abdel-Hadi S. Integration of hepatitis B immunization in the Expanded Program on Immunization of the Child Survival Project. *J. Egypt Public Health Assoc.* 1993; 68: 487-494.
- [14] Jara P, Bruguera M. Hepatitis B in pregnant women and children. *Enferm. Infecc. Microbiol. Clin*. 2008; 7: 66-70.
- [15] Field A. *Discovering statistics using IBM SPSS statistics*. (4th ed.). London, California, New Delhi: SAGE Publications Ltd 2013.
<https://studentvip.com.au/books/9781446249178>
- [16] World Health Organization. Emergencies preparedness, response: hepatitis: frequently asked questions https://www.who.int/health-topics/hepatitis#tab=tab_1.

- [17] Castelli R, Ferraris L, Pantaleo G, Deliliers GL, Cicardi M. High rate of hepatitis B viral breakthrough in elderly non-Hodgkin lymphomas patients treated with rituximab based chemotherapy. *Digestive and Liver Disease*. 2016; 48: 1394-1397.
- [18] Ismail SA, Cuadros DF, Benova L. Hepatitis B in Egypt: a cross-sectional analysis of prevalence and risk factors for active infection from a nationwide survey. *Liver International*. 2017; 37: 1814-1822.
- [19] Fekry MM, Hashish MH, Selim HS, Fawzy A, Wahba MM. Prevalence of hepatitis B virus among pregnant women attending antenatal care in Alexandria. *Journal of High Institute of Public Health*. 2019; 49: 175-179.
- [20] Kishk R, Mandour M, Elprince M, Salem A, Nemr N, Eida M, et al. Pattern and interpretation of hepatitis B virus markers among pregnant women in North East Egypt. *Brazilian Journal of Microbiology*. 2020; 51: 593-600.
- [21] Gad MA, Metwally MA, Eissab HA, Gehad MA, Rayand MM. Antenatal screening for hepatitis B virus infection. *Benha Medical Journal*. 2017; 34: 113-118.
- [22] Makhlof NA, Morsy K, Othman ER, Nasr Eldin E. Antenatal screening of pregnant women for hepatitis B virus infection in Upper Egypt: A Tertiary Care Center Based Study. *Egyptian Liver Journal*. 2014; 4: 57-62.
- [23] Gasim GI, Murad IA, Adam I. Hepatitis B and C virus infections among pregnant women in Arab and African countries. *Journal of Infection Developing Countries*. 2013; 7: 566-578.
- [24] Bani I, Mahfouz MS, Maki E, Gaffar A, Elhassan I, Yassin AO, et al. Prevalence and risk factors of hepatitis B virus among pregnant women in Jazan Region-Kingdom of Saudi Arabia. *Journal of Biology and Agriculture Healthcare*. 2012, 2: 39-44.
- [25]. Taseer IU, Ishaq F, Hussain L, Safdar S, Mirbahar AM, Faiz SA. Frequency of anti-HCV, HBsAg and related risk factors in pregnant women at Nishtar Hospital, Multan. *Journal of Ayub Medical College*. 2010; 22: 13-16.
- [25] Elsheikh RM, Daak AA, Elsheikh MA, Karsany MS, Adam I. Hepatitis B virus and hepatitis C virus in pregnant Sudanese women. *Virology Journal*. 2007; 4: 104.
- [27]. Shedain PR, Devkota MD, Banjara MR, Ling H, Dhital S. Prevalence and risk factors of hepatitis B infection among mothers and children with hepatitis B infected mother in upper Dolpo, Nepal. *BMC infectious diseases*. 2017; 17: 667
- [26] Elkhattab R, Kamel HH. Prevalence of hepatitis B and C in pregnant ladies and their neonates in Minya governorate. *Int. J. Pregn. & Chi. Birth*. 2018; 4: 71-73.
- [27] Metaferia Y, Dessie W, Al I, Amsalu A. Seroprevalence and associated risk factors of hepatitis B virus among pregnant women in southern Ethiopia: a hospital-based cross-sectional study. *Epidemiology and Health*. 2016; 38: e2016027
- [28] Alrowaily MA, Abolfotouh MA, Ferwanah MS. HBV seroprevalence among pregnant females in Saudi Arabia. *Saudi. J. Gastroenterol*. 2008; 14: 70-72.
- [29] Yohanes T, Zerdo Z, Chufamo N. Seroprevalence and predictors of hepatitis B virus infection among pregnant women attending routine antenatal care in Arab Minch Hospital, South Ethiopia. *Hepatitis Research and treatment*. 2016; 2016: 9290163.
- [30] Buseri F, Seiyaboh E, Jeremiah Z. Surveying infections among pregnant women in Niger Delta, Nigeria. *J. Glob. Infect. Dis.;* 2010, 2, 203-211.
- [31] Azhar T, Khan IA, Mohsein S, Usman J. Antenatal screening for hepatitis B and C virus infection in pregnant women in a tertiary care hospital of Rawalpindi. *Pakistan Armed Medical Journal*. 2011: 61: 1-5.
- [32] Ajayi AO, Komolafe AO, Ajumobi K. Sero-prevalence of Hepatitis B among health care workers in a Nigerian tertiary health institution. *Nigerian Journal of Clinical Practice*. 2007; 10: 287-289.
- [33] Eke AC, Eke UA, Okafor CI, Ezebialu IU, Ogbuagu C. Prevalence correlates and pattern of hepatitis B surface antigen in a low resource setting. *Virol. J*. 2011; 8: 12.
- [34] Sharifi-Mood B, Keykha F, Moghaddam ES, Salehi M, Kouhpayeh HR, Nayini RA, et al. Prevalence of hepatitis B surface antigen in pregnant women in Zahedan, Iran. *Hepat. Mon*. 2004; 4: 161-163.
- [35] Vazquez-Martinez JL, Coreno-Juarez MO, Montano-Estrada LF, Atllan M, Gomez-Dantes H. Seroprevalence of hepatitis B in pregnant women in Mexico. *Saud. Publica. Mex*. 2003; 45: 165-170.
- [36] Khalil MK, Al-Mazrou YY, Al-Jeffri M, Al-Ghamdi YS, Mishkhas A, Bakhsh M, et al. Serosurvey of hepatitis B surface antigen in pregnant Saudi women. *East. Mediterr. Health. J*. 2005; 11: 640-647.
- [37] Ahmadi M, Toghiani R, Shaidi S, Izadi M, Merasi Mr, Agdak P, et al. The study of prevalence of antigen HBs positive and high risk behaviors in pregnant women referring to urban health centers of Isfahan Province in 2009. *Iran J. Nurs. Midwifery. Res*. 2011; 16: 1-8.
- [38] Pereira LM, Martelli CMT, Merchán-Hamann E, Montarroyos UR, Braga MC, de Lima MLC, et al. Hepatitis Study Group. For the Hepatitis Study Group. Population based multicentric survey of hepatitis B infection and risk factor differences

- among three regions in Brazil. *Am. J. Trop. Med. Hyg.* 2009; 81: 240-247.
- [39] Elsabaawy MM, Elsherefya ME, Sakra HE, Elsabaawy D, Elshazly H, Elezaawyc H, et al. Current characteristics of chronic hepatitis B in Egypt. *Egypt. J. Intern. Med.* 2020; 31: 822-830.
- [40] Elzayadi AR, Ibrahim EH, Badran HM, Saeid A, Moneib NA, Shemis MA, et al. Anti-HBc screening in Egyptian blood donors reduces the risk of hepatitis B virus transmission. *Transfus. Med.* 2008; 18: 55-61.
- [41] Abdo A, Sanai F, Al-Faleh FZ. Epidemiology of viral hepatitis in Saudi Arabia: are we off the hook? *Saudi. J. Gastroenterol.* 2012; 18: 349-357.
- [42] Alavian SM, Hajarizadeh B, Ahmadzad-Asl M, Kabir A, Lankarani KB. Hepatitis B virus infection in Iran: a systematic review. *Hepatitis Monthly.* 2008; 8: 281-294.
- [43] Al-Naamani K, Al-Maqbali A, Al-Sinani S. Characteristics of hepatitis B infection in a sample of Omani patients. *Sultan Qaboos Univ. Med. J.* 2013; 13: 380-385.
- [44] Zarski JP, Marcellin P, Leroy V, Trepo C, Samuel D, Ganne-Carrie N, et al. Fédération nationale des Pôles de référence et des Réseaux Hépatites. Characteristics of patients with chronic hepatitis B in France: predominant frequency of HBe antigen negative cases. *J. Hepatol.* 2006; 45: 355-360.
- [45] Raptopoulou M, Papatheodoridis G, Antoniou A, Ketikoglou J, Tzourmakliotis D, Vasiliadis T, et al. Epidemiology, course and disease burden of chronic hepatitis B virus infection. HepNet study for chronic hepatitis B: a multicentre Greek study. *J. Viral. Hepat.* 2009; 16: 195-202.
- [46] Torre F, Basso M, Giannini EG, Feasi M, Boni S, Grasso A, et al. Clinical and virological survey of patients with hepatitis B surface antigen in an Italian region: clinical considerations and disease burden. *J. Med. Virol.* 2009; 81: 1882-1886.
- [47] Mota A, Guedes F, Areias J, Pinho L, Cardoso MF. Epidemiological study of genotypes of hepatitis B virus in northern Portugal. *J. Med. Virol.* 2009; 81: 1170-1176.
- [48] Rodriguez-Frias F, Jardi R, Buti M, Schaper M, Hermosilla E, Valdes A, et al. Hepatitis B virus genotypes and G1896A precore mutation in 486 Spanish patients with acute and chronic HBV infection. *J. Viral. Hepat.* 2006; 13: 343-350.
- [50] Mello FCA, Souto FJD, Nabuco LC, Villela-Nogueira CA, Coelho HSM, Franz HCF, et al. Hepatitis B virus genotypes circulating in Brazil: molecular characterization of genotype F isolates. *BMC Microbiol.* 2007; 7: 103-111.