RESEARCH ARTICLE

Serological Screening for HBV Infection in Pregnancy Results and Obstetric and Neonatal Outcomes in 45,000 Pregnant Women

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Abstract

Objective: The study evaluates the trend over time and the results of serological screening for Hepatitis B infection in pregnancy and obstetric and neonatal outcomes.

Study design: It is a retrospective observational study of all pregnant women delivered in maternity units in Trento province, North East Italy, between 2009-2018. Serological screening data for hepatitis B virus were collected through the birth attendance certificate that is the mandatory tool in Italy for the birth report and the monitoring of the pregnancy, childbirth and health of the new-born. Dell’Anna L, et al. used the information collected from the Hospital information system in order to get, for confirmed positive cases, the data of the entire serological profile. On this basis, dell’ Anna L, et al. calculated the coverage of serological screening, the seroprevalence of the infection and the maternal and neonatal outcomes.

Results: A total of 45,493 pregnant women were analysed, 75.5% Italians and 24.5% foreigners. The mean coverage for serological HBV screening in pregnancy was 99.5%. 365 HBsAg positive pregnant women were identified (41 Italians and 324 foreigners). Mean overall infection seroprevalence was 8.0‰ (95% CI: 7.7-8.3); amongst Italians it was 1.2‰ (95% CI: 1.1-1.3) and amongst foreigners it was 28.0‰ (95% CI: 27.6-28.4). The highest seroprevalence was recorded in mothers coming from Eastern European countries. In HBsAg positive mothers there was no evidence of any excess pregnancy-related comorbidity compared to HBsAg negative mothers. In particular no excess in gestational diabetes was observed. In HBsAg positive mothers, less recourse to elective caesarean delivery or in labour than in HBsAg negative mothers are observed even if the differences are not statistically significant. In infants from HBsAg positive mothers, there is only a statistically significant excess of cases undergoing resuscitation procedures compared to those born to HBsAg negative mothers. We do not record any other differences between infants of HBsAg positive and HBsAg negative mothers. All infants of HBsAg positive mothers underwent passive and active immunization procedures at birth.

Conclusions: The information collected by the birth attendance certificate can be used to verify the compliance with national recommendations on the serological screening of hepatitis B virus infection in pregnancy. Foreign mothers have a prevalence of infection 3 times higher than Italian mothers. This reflects the previous vaccination policies followed in different countries. In relation to the obstetric-neonatal indicators evaluated, there are no significant differences between HBsAg positive mothers and HBsAg negative mothers.

Keywords: Pregnancy, Serological screening, HBV infection, Obstetric and Neonatal Outcomes

Introduction

Chronic Hepatitis B virus (HBV) infection affects about 350 million individuals worldwide and in 15-40% of infected subjects, progression of the disease to cirrhosis, liver failure or hepatocellular carcinoma is possible [1]. In endemic areas, the infection is acquired in 50% of cases in the perinatal period or in early childhood from mothers with chronic HBV infection, with a risk of chronicization of 90% and 20-30% respectively [2]. Vaccination against Hepatitis B of all infants, during the first year of life, is a fundamental measure for the prevention of the disease [3]. Another cornerstone of disease prevention is the monitoring of HBV infection in pregnancy [4]. An acute HBV infection in pregnancy does not generally have a

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complicated course and is not associated with an increase in stillbirth or fetal malformations. The risk of transmission to the fetus increases as pregnancy progresses, from 10% in the case of infections in the first trimester to 60% in the case of infections contracted in the third trimester [4-6]. Serological screening for HBV through the determination of HBsAg is a universally recommended practice and in Italy, this assessment is one of the prenatal screenings provided for all pregnant women. It is free of charge and to be carried out normally during the third trimester [7]. Screening for the infection during pregnancy makes possible to offer HBV vaccination to all unvaccinated mothers with risk factors for hepatitis B and, if the mother is found to be positive, to provide the infant with passive and active prophylaxis, reducing the transmission rate from 90% to 5-10% [4-6]. In the case of high maternal viremia levels (> 200,000 IU/mL), treatment of the pregnant woman with antiviral drugs is also recommended during the third trimester of pregnancy and until delivery [8,9]. The registration of the serological assessment of HBV infection in pregnancy has been carried out systematically in the province of Trento since the 2000s, through the Birth Assistance Certificate (BAC). The BAC is the mandatory document in Italy for the notification of birth and the monitoring of pregnancy, birth and the health of the newborn [10]. This study reports the trend of HBV infection screening among pregnant women assisted at the maternity units of the province of Trento (north east Italy, 540,000 inhabitants as of 31.12.2018) from 2009 to 2018, analyzing the coverage, the characteristics of cases ascertained as positive, obstetric and neonatal outcomes.

Materials and Methods

Screening for HBV in pregnancy is performed using an HBsAg assay, with a confirmation test in the case of a positive result, and HBcAg and anti-HBc antibody assays if positivity is confirmed [7]. This is followed by the determination of the viral load on the plasma. If the HbsAg determination is not made during the third trimester, it must be carried out in an emergency regime during hospitalization for childbirth and in any case not later than 48 hours after birth. The purpose of these measures is to guarantee timely immunisation of at-risk infants and to minimise the risk of vertical transmission of the infection. The result of the first level test of serological screening for B virus infection, that is, the presence / absence of HBsAg is recorded in the model of BAC in use in the province of Trento. The HBsAg test result is recorded as: a) test not performed; b) negative test, c) positive test, d) test in progress or e) vaccinated subject. All BAC data are recorded on a storage device at each maternity units by the midwives present at the birth. The annual archive for all births assisted at the maternity units of the province is subsequently made available for the Clinical and Evaluational Epidemiology Service of the Provincial Health Authority for data control, transfer to the regional authorities and preparation of standard birth rate reports. Cases with positive test outcomes or tests in progress were checked through the Hospital Information System (HIS), an electronic repository containing the results of all contacts between resident and non-resident users and the healthcare facilities of the province of Trento. Access to the hospital information system also made possible to retrieve the complete serological profile envisaged in the case of HBsAg positivity, namely the HBeAg, anti-HBe and anti-HBc antibody and viral load assays. With regard to this last aspect, data was also acquired regarding any treatment of the pregnant women during pregnancy. The BAC data and the additional data retrieved through the HIS were used to calculate compliance with serological screening during pregnancy and the seroprevalence of the infection, also in terms of the nationality, age range and educational level of the mother. The sections of the BAC regarding maternal disease and infant health were used to investigate maternal morbidity in pregnancy and the neonatal outcomes, by performing a comparison between infants born to HBsAg-positive mothers and those born to HBsAg-negative mothers. For each baby born to an infected mother, the HIS was consulted to ascertain whether the active and passive immunisation procedures had been performed and to acquire data regarding the monitoring of HBsAg in the first 6 months after the birth. Trend significance was analysed using the Cochran-Armitage criterion and the significance of the differences between the subpopulations compared was analysed using the Chi-squared test or Fisher’s exact test. The prevalence estimates are provided with 95% confidence intervals.

Results

A total of 45,493 pregnant women were evaluated, of which 75% were Italian citizens (average age 33 years) and 25% were foreigners (average age 28.7 years). The proportion of foreign pregnant women rose from 23.3% in 2009 to 26.3% in 2018. The corresponding number of live births for the same period was 46,145. Average coverage of serological HBV screening in pregnancy over the study period was 99.5%, without any variations between one year and another. There are no statistically significant differences in coverage, in relation to citizenship, age group and education level. During the study period, 365 HBsAg-positive pregnant women were identified (41 Italians and 324 foreigners), 36.5 cases on average per year, with a progressive decrease over time (Figure 1) of -4.4% per year. The mean overall seroprevalence in pregnant women was 8.0‰ (95% CI: 7.7-8.3); amongst Italian women it was 1.2‰ (95% CI: 1.1-1.3) and amongst foreigners it was 28.0‰ (95% CI: 27.6-28.4), with a statistically significant difference (p<0.0001). In foreigners the serum prevalence is higher in mothers from Eastern European countries (37.2 %) with a statistically significant difference (p<0.001) compared to the average values of foreigners. In the last two years of the study period, the serum prevalence shows a reduction compared to the average values of the entire period but it is reduced less than the absolute cases due to the reduction in pregnancies (Figure 1). Seroprevalence is statistically significantly higher (p<0.05) in the 20-24 and 25-29 years age ranges (Figure 2) and amongst mothers with low education level (Figure 3). The average age of HBsAg-positive women was 28.8 years (28.0 amongst foreigners and 36.0 years among Italians) without any relevant variations from one year to another. In 5 cases,
Figure 1: Province of Trento, HBsAg + cases per year and seroprevalence of HBV infection/1000 pregnant women. Period 2009-2018.

Figure 2: Province of Trento, Seroprevalence of HBV infection/1000 pregnant women by age class. Period 2009-2018.

Figure 3: Province of Trento, Seroprevalence of HBV infection/1000 pregnant women by educational level. Period 2009-2018.
concomitant positivity was observed for HCV, in 2 cases for cytomegalovirus (CMV) and in 2 cases for toxoplasmosis. In the Italian women, the prevalent clinical condition was chronic or inactive carrier (73.1%), whereas amongst the foreigner’s prior hepatitis B virus infections prevailed (63.8%). The acute forms of infection (4.3% of all cases) almost exclusively regarded foreign women (Table 1). All pregnant women with high viremia levels (> 200,000 IU/mL) equal to 7 cases (1.9% of the total of HBsAg positive mothers) were treated with antiviral drugs during pregnancy. The antiviral of election is currently Tenofovir, a safe agent that, unlike the antivirals used in the past, does not lead to the development of resistance. The analysis of the conditions that developed during pregnancy did not allow highlighting any significant differences between HBsAg-positive and HBsAg-negative mothers. In particular, there was no excess of gestational diabetes that recurs in the former with a lower frequency than in the latter: 32.8/1000 vs. 45.6/1000. With regard to obstetric indicators, in positive HBsAg mothers there is less recourse to elective caesarean delivery or in labour than in negative HBsAg even if the differences are not statistically significant. In mothers with high viremia, vaginal birth is also used in 9 out of 10 cases. As regards neonatal indicators, we report, in those born to HBsAg positive mothers, only a statistically significant excess (p<0.05) of newborns subjected to resuscitation procedures compared to those born to HBsAg negative mothers (Table 2). We find no difference in neonatal indicators in relation to the initial maternal viral load. 98% of infants born to HBsAg-positive mothers were evaluated regarding the performance of passive/active prophylaxis at birth. All subjects were treated in accordance with the protocol, without any difference between Italian and foreign women. The 2% of cases that were not assessed regarded mothers that were not resident in the province of Trento.

Conclusions

The recording of serological screening data for HBV infection in pregnancy based on the BAC appears a convenient approach for an area-based assessment. The local availability of an information repository such as the HIS is in any case essential in order to also have a full serological profile for HBsAg-positive women and therefore for evaluating the opportunity of administering treatments during pregnancy. The coverage of serological screening in pregnancy for HBV infection includes virtually all assisted pregnant women in the province of Trento, without any difference in relation to age, education level and citizenship. Screening coverage appears to be higher than that reported in previous Italian studies and would appear to guarantee, at local level, equal access to serological screening, regardless of the woman’s characteristics in terms of nationality [11,12]. The framework also indicates full application at local level of what is indicated by the National Guidelines on pregnancy care [7]. The average seroprevalence referred to all pregnant women corresponds to that of a low-endemic area [13] and it is similar to that reported in a previous Italian multicentre study [11]. The difference in serum prevalence between Italians and foreigners appears to be very high, greater than previously reported for Italy [11] but consistent with more recent Italian studies [12,14]. The differences are also the result of the different vaccination policies developed in previous decades, in different countries, towards the general population and should reduce over time with the optimization of the vaccination offer in countries with the greatest endemic. A certain level of attention must be maintained not only with regard to the migrant populations, but also to younger pregnant women and those with a lower level of education. HBV infection acquired during pregnancy can have effects on the health of both the mother and the offspring. Pregnancy can also affect the course of HBV infection [15,16].

Table 1: Province of Trento. Clinical condition of HBsAg positive mothers. Overall and by citizenship. Period 2009-2018.

<table>
<thead>
<tr>
<th>Clinical conditions</th>
<th>Italians</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>%</td>
<td>Number</td>
<td>%</td>
<td>Number</td>
</tr>
<tr>
<td>Acute hepatitis B</td>
<td>1</td>
<td>2.4</td>
<td>15</td>
<td>4.6</td>
<td>16</td>
</tr>
<tr>
<td>Chronic hepatitis B</td>
<td>1</td>
<td>2.4</td>
<td>18</td>
<td>5.6</td>
<td>19</td>
</tr>
<tr>
<td>Past infection</td>
<td>9</td>
<td>22.0</td>
<td>207</td>
<td>63.9</td>
<td>216</td>
</tr>
<tr>
<td>Chronic virus B carrier</td>
<td>16</td>
<td>39.0</td>
<td>55</td>
<td>17.0</td>
<td>71</td>
</tr>
<tr>
<td>Inactive carrier of the hepatitis B virus</td>
<td>14</td>
<td>34.1</td>
<td>29</td>
<td>9.0</td>
<td>43</td>
</tr>
<tr>
<td>Total</td>
<td>41</td>
<td>100.0</td>
<td>324</td>
<td>100.0</td>
<td>365</td>
</tr>
</tbody>
</table>

Table 2: Province of Trento. Neonatal outcomes according HBsAg status of the mothers. Period 2009-2018.

<table>
<thead>
<tr>
<th>Neonatal indicators</th>
<th>Infant from HBsAg positive mothers</th>
<th>Infant from HBsAg negative mothers</th>
</tr>
</thead>
<tbody>
<tr>
<td>stillbirth</td>
<td>2.7‰</td>
<td>2.9‰</td>
</tr>
<tr>
<td>% newborn from elective caesarean section</td>
<td>15.6%</td>
<td>18.9%</td>
</tr>
<tr>
<td>% newborn from caesarean delivery in labor</td>
<td>4.0%</td>
<td>6.3%</td>
</tr>
<tr>
<td>% newborns preterm</td>
<td>5.2%</td>
<td>6.4%</td>
</tr>
<tr>
<td>% low birth weight (&lt;2500 g)</td>
<td>3.5%</td>
<td>7.1%</td>
</tr>
<tr>
<td>average Apgar score at 5</td>
<td>9.6</td>
<td>9.6</td>
</tr>
<tr>
<td>% hospitalized at birth</td>
<td>15.1%</td>
<td>11.9%</td>
</tr>
<tr>
<td>% resuscitation treatment at birth</td>
<td>7.5%</td>
<td>4.8%</td>
</tr>
<tr>
<td>% breast feed</td>
<td>86.7%</td>
<td>82.6%</td>
</tr>
</tbody>
</table>
Most women with chronic HBV infection present, in our study, a stable disease during pregnancy, often associated with a normalisation of transaminase values, as already reported in the literature [2,6,17]. Acute HBV infection itself during gestation is usually not serious and is not associated with increased mortality or teratogenicity and therefore should not lead to termination of pregnancy [18,19]. There are no definite associations between chronic HBV infection and the development of other diseases during pregnancy. Based on what is recorded in the BAC we use, we do not report any difference in maternal morbidity between HBsAg positive and HBsAg negative pregnant women. More specifically, our data did not confirm the increase in gestational diabetes reported by previous studies [20,21]. The impact of maternal HBV infection on infants has not been systematically studied. The most important risk factor for perinatal transmission of HBV, despite proper management of prophylaxis, is represented by the high viremia of the mother. Adequate antiviral treatment in pregnancy of all mothers with high viremia contributes significantly to reducing the risks of transmitting the infection to the fetus [2,4,6]. The results of our study appear to be consistent with those of a previous large retrospective study that compared 824 HBsAg-positive women with 6,281 HBsAg-negative controls, with no differences being observed in terms of gestational age, birth weight, congenital abnormalities or perinatal mortality [22]. Our study did not confirm higher premature birth or low birth weight rates as reported in two previous studies on mothers with acute HBV infection [19,23]. The more frequent hospitalisations at birth for infants born to HBsAg-positive mothers could at least in part be attributed to the need to complete the active and passive prophylaxis procedures required prior to discharge. All newborn born from HBsAg+ mothers for whom data were available were treated with hepatitis B vaccine and specific immunoglobulins (HBIG) within the first 12 hours of life. The advantage of caesarean delivery in protecting against the transmission of infection to the fetus has not been clearly established, the obstetric approach should therefore not be influenced by the mother’s HBV status [2,24]. Breastfeeding should also be encouraged, which can also be continued in women who need to continue treatment in the puerperium [4-6]. The use of caesarean delivery, both in election and in labour, in our study, is lower in HbsAg positive mothers than in HbsAg negative mothers even if the differences are not statistically significant. The choice of the type of birth seems to be oriented, at least in part, by the viremic load of the mother. The choice of the type of birth can however be dictated on the basis of other conditions or needs. It should also be borne in mind that the series considered in our study is characterized by a high prevalence of previous infections with a low level of transmissibility.

Conflicts of Interest
The authors have nothing to disclose.

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