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CHRONIC HEPATITIS B AND C IN WOMEN: COURSE OF PREGNANCY, DELIVERY AND MORPHOLOGICAL CHARACTERISTICS OF THE PLACENTA

Abstract

Despite the widespread global prevalence of chronic hepatitis, the impact of these diseases on the pregnancy course and on delivery is still insufficiently studied. Recently, some studies have been published, discussing the relationship between the state of the placenta and the risk of the mother-to-child transmission of hepatitis. The objective of this work was to make a comparative analysis of the features of pregnancy in women with chronic hepatitis B and C (CHB and CHC, respectively), to evaluate the relationship between inflammatory changes in the placenta and the frequency of hepatitis markers detection in umbilical cord blood. In this work we present a retrospective analysis of randomly selected birth histories of women with chronic hepatitis, from the Maternity Hospital No. 16 in St. Petersburg. In total, 35 pregnant women with CHB and 36 pregnant women with CHC were included in this study. Exclusion criteria were co-infections, cirrhosis and severe concomitant diseases. The studied groups had no significant differences in age, weight and height, as well as in the number of pregnancies and deliveries in their medical history. According to the results of our study, there were no significant differences in the state of newborns of mothers with CHB and CHC. According to our data, anemia during pregnancy occurred significantly more frequently in women with CHB, than with CHC. It has been shown that in both groups, the choriodeciduitis was observed in almost a half of women. Remarkably, the frequency of premature rupture of membrane in both groups was significantly higher than the average in the population. In addition, a reliable relationship between inflammatory changes in the placenta and the detection of HBsAg in umbilical cord blood was revealed. This relationship suggests that in women with inflammatory changes in the placenta, the risk of hepatitis B vertical transmission may be higher.

Key words: *chronic hepatitis B and C, placenta, inflammatory changes*

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HBV — hepatitis B virus, HCV — hepatitis C virus, PRM — premature rupture of membranes, ERM — early rupture of membranes, CHB — chronic hepatitis B, CHC — chronic hepatitis C

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Introduction

Despite the progress made in recent years, chronic hepatitis B (CHB) and hepatitis C (CHC) remain a serious health problem. Hepatitis B virus (HBV) and hepatitis C virus (HCV) infection differs significantly between regions. The infection rate in pregnant women generally corresponds to the average infection rate in the population of this region.

In Europe the prevalence of HBsAg in pregnant women can range from 0.1 % in the Northwest to 1–4 % in the South. In the Russian Federation (RF) frequency of HBsAg in pregnant women was 0.5 % in 2015 [1].

The prevalence of HCV infection in pregnant women in Europe ranges from 1 to 2.5 % [2]. In Russia the detection rate of anti-HCV antibodies in pregnant women was 2.8 % in 2002 [3]. According to official statistics, in some regions of the Russian Federation the number of pregnant women with anti-HCV antibodies in the blood is now 3–5 times higher compared to 2000-2001. Currently, the examination for HBsAg and anti-HCV antibodies in the first and third trimesters of pregnancy is regulated by the order of the Ministry of Health of the Russian Federation No. 572n dated 1.11.2012 [4].

To date, the effect of pregnancy and childbirth on the course of CHB has not been sufficiently studied. It is believed that women usually tolerate pregnancy well with underlying CHB in the absence of cirrhotic remodeling of the liver. During pregnancy there are generally no exacerbations of CHB, cytolytic activity parameters are often normalized. In Russia, the course of CHB during pregnancy was studied only in some regions. A fairly detailed study was conducted in the Republic of Sakha (Yakutia) [5, 6]. It was shown that clinical manifestations of CHB in pregnant women were characterized by a predominance of asthenic-vegetative and dyspeptic syndromes (63 %). Hemorrhagic syndrome in the form of bleeding gums was observed in 15 % of women and hepatomegaly occurred in 10 % [7]. It is well known that when there is no specific immunologic prophylaxis, the risk of vertical HBV transmission from HBsAg-positive mothers can reach 90 % [8]. It has been shown that HBsAg easily overcomes the utero-placental barrier [9] and is often found in umbilical cord blood in children born to HBsAg-positive mothers. At the same time, HBsAg is not always found in the umbilical cord blood. The reasons why in some cases the placenta becomes permeable to HBsAg are not well understood. Recent studies have actively studied the relationship between HBV and HBsAg detection in the placenta and vertical HBV transmission rate [10, 11]. It has been shown that there is a statistically significant association between HBsAg detection in newborns and the presence of HBsAg in the placenta. There were significantly higher risks of infection transmission in the case of infection in cells of villous endothelium [11].

CHC infection in a woman usually does not have a significant impact on the course of pregnancy. There are studies indicating a higher incidence of gestational diabetes in HCV-infected women compared with HCV-negative women, but this trend is significantly more pronounced in women with excessive weight gain during pregnancy, while increased incidence of gestational diabetes was not observed in women with insufficient or adequate weight gain. Some authors note the relationship between the presence of CHC and premature rupture of membranes [12]. In addition, it was found that the presence of CHC in the mother is more often associated with the birth of low-weight children [12]. It has also been shown that children born to mothers with CHC are more likely to require mechanical ventilation [12]. However, there are certain difficulties in evaluation of the effect of CHC in the mother in particular, since in order to obtain reliable results the impact of other factors such as drug use has to be excluded. Recent studies in large groups of patients have shown that CHC increases the risk of premature birth, low birth weight, premature rupture of membranes, as well as the risk of gestational diabetes in the mother and birth defects in babies [12–16]. In addition, there are studies indicating that HCV infection in the mother may be associated with more frequent development of cholestasis in pregnant women [13, 15].

Large population studies have shown that there is a relationship between CHC in the mother and premature birth [13, 16]. However, it should be borne in mind that premature birth can be induced by other factors. In the study conducted by L. E. Connell et al. [13] a multivariate statistical analysis that included factors such as drug use, tobacco use, and

alcohol use was performed. In this study, it was shown that patients with CHC had a greater risk of premature birth [13]. In addition, the same study showed that children born to mothers with CHC are more likely to have lower birth weight and malformations. In a study conducted in New Mexico [15] premature birth (up to 37 weeks of gestation) was significantly more common in HCV-positive women (24.5 % vs. 14.9 %), but multivariate analysis showed that differences cease to be significant when excluding methadone use, smoking and previous premature birth in history.

In 2011, the results of a large population-based study conducted in the United States from 1998 to 2007 were published, and in this study the incidence of perinatal complications in women with and without CHB and CHC was analyzed [13]. Significant differences were demonstrated in the frequency of premature rupture of membranes with and without CHB. It was shown that gestational diabetes was significantly more likely to develop in women with CHB and CHC than without these infections. In addition, anemia during pregnancy is also more common in women with CHB and CHC. The incidence of anemia in pregnant women differs significantly in different countries. In Europe, according to WHO, anemia in pregnant women occurs in 18.6–31.6 % of cases, while in Africa this figure is 52.8–61.3 % [17]. At the same time, anemia in pregnant women in developed countries occurs on average in 14 %, while in developing countries this figure may be 59 % [18].

In full-term pregnancy premature rupture of membranes occurs in 2.7–17 % of cases [19]. At the same time, this figure is significantly higher in premature birth. Prenatal rupture of membranes accompanies preterm birth in up to 30–56 % of cases [19–21]. Premature rupture of membranes (PRM) is considered to be the rupture of membranes before birth regardless of the pregnancy period. Early rupture of membranes (ERM) is indicated in the case of rupture of the membranes after the beginning of delivery, but before the cervix is completely opened [22]. English-language literature has adopted the term premature rupture of membranes which combines both these concepts. In Russian-language literature, there are very little data on the incidence of this complication of pregnancy in women with chronic hepatitis.

Placental insufficiency is a syndrome that occurs in various diseases of the mother and fetus with manifestations in the form of molecular, cellular, tissue and organ disorders in the mother-placenta-fetus system. Placental insufficiency can be compensated, subcompensated and decompensated. The incidence of placental insufficiency in pregnant women with chronic hepatitis is insufficiently studied.

Inflammatory changes in the placenta are common in various diseases, but can also occur in apparently healthy women [23]. These changes may cause septic complications in the postnatal period in the mother, and they may also cause various pathological conditions in the newborn. Data on the frequency of histologically confirmed inflammatory processes in the placenta are contradictory: according to different authors, they are found in 5 % to 40 % of all full-term pregnancies.

Chronic deciduitis occurs in 15 to 41 % of cases [24], and is much more common in premature birth. According to Russian authors, choriodeciduitis is found in 21.7±2.4 % of timely birth cases [25]. The relationship between the presence of inflammatory changes in the placenta and vertical transmission rate is insufficiently studied. The objective of this work was to conduct a comparative analysis of pregnancy features in women with CHB and CHC, and to assess the relationship between inflammatory changes in the placenta and the frequency of detection of hepatitis markers in the umbilical cord blood.

Materials and methods

This study employed a retrospective analysis of randomly selected labor and delivery medical records of women who gave birth in the maternity hospital No. 16 in St. Petersburg (Chief Medical Officer — MD, prof. Shapkayts V. A.) in 2014–2015.

The study included 35 pregnant women with CHB (mean age of 30.46±1.53 years) and 36 pregnant women with CHC (mean age of 33.47±1.17 years). All women included in the study had a full-term pregnancy. All women underwent standard clinical and biochemical studies regulated by documents for pregnancy management. In addition, umbilical cord blood was tested for HBsAg in patients with CHB, and umbilical cord blood was

tested for anti-HCV antibodies in women with CHC. Blood sampling was carried out from the umbilical vein immediately after birth. The studies were conducted at the City Virology Diagnostic Center (Chief Medical Officer — Vashukova S. S., Can.Med.Sci.). For HBsAg detection, the HBsAg-confirming-ELISA-BEST reagent kit manufactured by Vector Best (sensitivity of 0.01 IU/ml) was used for immunoassay to confirm the presence of HBsAg. Anti-HCV antibodies in umbilical cord blood were determined using the reagent kit for immunoassay detection of anti-HCV immunoglobulins from G and M classes for automatic immunoassay analyzers Best anti-HCV-auto (manufacturer — Vector Best).

Assessment of fibrosis degree during pregnancy was not carried out (transient elastography is contraindicated, liver biopsy is undesirable, FibroTest is uninformative due to altered hormonal background). However, the women included in the study had no clinical signs of advanced stages of liver fibrosis.

Histological examination of the placenta was carried out in hospital No. 16.

The exclusion criteria were: co-infection with HIV, mixed hepatitis caused by CHB and CHC, co-infection with hepatitis Delta, premature birth, cirrhotic stage of chronic hepatitis, syphilis, clinically expressed diseases of the urogenital tract.

For assessment of the statistical significance of differences between groups for qualitative features, χ-square test was used, including Fisher's correction for small samples, and Mann-Whitney test was used for quantitative parameters. Differences were considered statistically significant with $p<0.05$.

Results

The clinical features of the examined women are presented in Table 1.

As shown in Table 1, examined patients with CHB and CHC had no significant differences in age, weight and height, the number of pregnancies and births in their history. Cesarean delivery was performed in 7 (20 %) women with CHB and in 1 (2.8 %) woman with CHC. The reasons for the operation in the group of pregnant women with CHB were: fetal hypoxia in 4 cases, myopia in the mother and/or large fetus in 3 cases. In the group of patients with CHC cesarean section was performed due to the presence of a scar on the uterus after previous cesarean section.

In the group of pregnant women with CHB only 4 (11.4 %) patients were HBsAg-positive. Data on viral load in pregnant women in the third trimester are presented in Table 2.

Pregnancy complications which were observed in examined women are presented in Table 3. The most common events were anemia, swelling in pregnant women and premature rupture of membranes.

Anemia during pregnancy was significantly more common in the group of women with CHB.

There were no statistically significant differences between the groups in the incidence of edema in pregnant women. In both groups, there was

Table 1. *Clinical characteristics of women with CHB and CHC in the studied groups*

Parameters	CHB n=35	CHC n=36	p
Height	164.97±1.69	163.89±1.62	0.33
Weight	77.63±5.92	73.09±4.15	0.83
Number of pregnancies	2.54±0.46	4.19±1.19	0.15
Number of births	1.74±0.28	1.97±0.28	0.25

Table 2. *Viral load in women with CHB and CHC in the third trimester of pregnancy*

	Median	1 quartile	3 quartile
CHB (IU/ml) n=18*	4,200	1,300	177,000
CHC (IU/ml) n=36	317,000	140,000	1,410,000

***** For 17 patients with CHB the data were not available.

Table 3. *Frequencies of the appearance of specific pregnancy complications*

Complication	CHB n=35	CHC n=36	p-value
Anemia	54.3% (19)	19.4% (7)	0.002*
Swelling during pregnancy	17.1% (6)	5.6% (2)	0.12
Premature rupture of membranes	42.9% (15)	55.6% (20)	0.29

***** Significant difference between the groups ($p<0.005$).

Table 4. *Main characteristics of newborns of mothers with CHB and CHC*

Parameters	CHB	CHC	p-value
Height	51.77±1.08	51.11±0.84	0.16
Weight	3,482±213.17	3,311.94±179.97	0.23
Apgar score (1 min)	7.57±0.2	7.58±0.2	0.94
Apgar score (5 min)	8.6±0.18	8.58±0.2	0.99

Table 5. *Relationship between inflammation in placenta and the HBsAg presence in umbilical cord blood*

	HBsAg+	HBsAg-	Total
Inflammation	14	6	20
No inflammation	3	12	15
Total	17	18	35

a significant incidence of premature and early rupture of membranes: 42.9 % — in the group with CHB and 55.6 % — in the group with CHC. There were no statistically significant differences between the groups in relation to this complication.

The duration of membrane rupture to delivery interval in the group with CHB was on average 411±242 min. In the group with CHC this parameter was 242±76 min. There were no significant differences in this parameter between groups.

The analysis of the state of newborns was carried out in the studied groups. There were no statistically significant differences in such parameters as height, weight, Apgar score (Table 4).

We studied the incidence of various inflammatory changes in the placenta of women with CHB and CHC. The examined women had the following inflammatory changes: choriodeciduitis, villitis, intervillositis, membranitis. Choriodeciduitis was the most common inflammatory process in placenta which was found in almost half of the women examined (48.6 % of women with CHB and 50 % of women with CHC). Other inflammatory changes in the placenta were significantly less common. There were no inflammatory changes in the placenta in 42.85 % of women with CHB and only in 33.3 % of women with CHC. There were no statistically significant differences between the groups in relation to any of these parameters.

The relationship between the presence of inflammatory changes in the placenta and HBsAg detection in umbilical cord blood was evaluated. The results are shown in Table 5.

For the data in Table 5 the value of $\chi 2$-test is 8.578, while the critical value of $\chi 2$ is 6.635 at the significance level of $p<0.01$. Thus, the relationship between the presence of inflammation in the placenta and the presence of HBsAg in umbilical cord blood is statistically significant at the significance level of $p<0.01$.

At the same time, anti-HCV antibodies were present in all umbilical cord blood samples taken from mothers with CHC regardless of the presence or absence of inflammatory changes in the placenta.

Results and discussion

Patients with CHB and CHC included in the study were comparable in terms of main clinical parameters (age, height, weight, number of pregnancies and births in history).

The results obtained in our study showed that anemia was significantly more common during pregnancy in women with CHB than in women

with CHC. It should be noted that no women included in the study had advanced stages of fibrosis, and therefore anemia could not be due to the severity of hepatitis. Thus, the mechanisms of anemia during pregnancy in women with CHB require further study.

Our data on the incidence of anemia during pregnancy in women with CHC are comparable with data on the incidence of anemia in pregnant women in European countries. At the same time, our study showed that anemia during pregnancy was significantly more common in women with CHB. This result is consistent with the data obtained by L. E. Connell et al., which also showed statistically significant differences ($p<0.0001$) in the frequency of anemia during pregnancy in women with and without CHB [13].

In this study, there were no significant differences in the incidence of swelling in pregnant women in the study groups.

The results obtained in this study indicate that the frequency of premature rupture of membranes in women with CHB and CHC did not differ significantly. It should be noted that the frequency of this pregnancy complication is significantly higher in the study groups than in the general population. This is consistent with the claims of other authors who noted the relationship between the presence of CHC in the mother and premature rupture of membranes [12]. In CHB, a higher rate of premature rupture of membranes was also recorded compared to patients without CHB ($p=0.01$) [13].

There were no significant differences in the status of newborns from mothers with CHB and CHC in the study groups. Newborns in the study groups did not differ in terms of such parameters as height and weight. Some studies have shown that the presence of CHB in the mother leads to the birth of children with lower Apgar scores [26, 27]. In this study, Apgar score at the first and fifth minutes did not have significant differences in the groups, and it was quite high. In addition, some studies [12, 13] indicate that the presence of CHB or CHC in the mother may lead to the birth of children with lower body weight, but the present study did not confirm this.

In a recent study, it was shown that the incidence of placental insufficiency in women with CHB and CHC is significantly higher than in women without hepatitis [28]. In the present study, it is shown that chronic compensated placental insufficiency was the most common in both groups. Conspicuous is the fact that a fully compensated placenta was identified only in 4 women with CHB and in none of the women with CHC.

This study also showed that there was a statistically significant relationship between the presence of inflammation in the placenta and the presence of HBsAg in the umbilical cord blood ($p<0.01$). The presence of any inflammatory process in the placenta leads to altered permeability, which in turn can increase the risk of vertical infection transmission.

Conclusions

1. Anemia during pregnancy was significantly more frequent in women with CHB than in women with CHC.
2. There were no significant differences in the rate of premature rupture of membranes between the study groups, but in both groups it was significantly higher than the average in the population.
3. There was a significant relationship between the presence of inflammatory changes in the placenta and HBsAg detection in umbilical cord blood. This relationship suggests that women with inflammatory changes in the placenta may have a higher risk of vertical HBV transmission.

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Conflict of interests

The authors declare no conflict of interests.

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