Meta-Analysis on Amniocentesis for Mother-to-Child HBV Vertical Transmission (Post-print)

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Abstract

Objective: Mother-to-child vertical transmission of hepatitis B virus has become the main route of HBV infection in China. This study analyzes whether amniocentesis in pregnant women infected with hepatitis B virus increases the risk of mother-to-child vertical transmission.

Methods: Relevant English or Chinese articles published between January 1, 1990 and March 15, 2016 were searched in databases including Pubmed, Embase, Google Scholar, and Wanfang Database regarding the impact of amniocentesis on mother-to-child vertical transmission in pregnant women with hepatitis B. Articles were screened according to inclusion and exclusion criteria, then assessed for methodological quality. Finally, 4 articles were included, with a total of 3997 pregnant women, including 167 in the experimental group and 3830 in the control group. Data analysis was performed using Review Manager Version 5.0.

Results: Meta-analysis results showed no significant difference in the positive rate of HBsAg between infants in the amniocentesis group and the non-amniocentesis group (OR = 1.37, 95% CI: 0.70–2.69, P = 0.36). When pregnant women had HBV-DNA 10 copies/mL or were HBeAg-positive, the risk of intrauterine infection increased after amniocentesis (OR = 9.54, 95% CI: 3.52–25.85, P < 0.0004; OR = 3.41, 95% CI: 1.05–11.13, P = 0.04).

Conclusion: Pregnant women with HBV-DNA 10 copies/mL and/or HBeAg positivity have an increased risk of mother-to-child vertical transmission.

Full Text

Preamble

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Meta-Analysis of Mother-to-Child HBV Transmission via Amniocentesis

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Abstract

Objective: Mother-to-child vertical transmission of hepatitis B virus (HBV) has become the primary route of HBV infection in China. This study investigates whether amniocentesis in HBV-infected pregnant women increases the risk of mother-to-child vertical transmission.

Methods: We searched PubMed, Embase, Google Scholar, and Wanfang databases for relevant English or Chinese articles published between January 1, 1990, and March 15, 2016. After screening according to inclusion and exclusion criteria and quality assessment, four articles were included, comprising 3,997 pregnant women (167 in the experimental group and 3,830 in the control group). Data analysis was performed using Review Manager Version 5.0.

Results: The meta-analysis showed no significant difference in infant HBsAg positivity rates between women who underwent amniocentesis and those who did not (R^2 = 1.37, 95% CI: 0.70–2.69, P = 0.36). However, when pregnant women had HBV-DNA 10 copies/mL or were HBeAg-positive, amniocentesis increased the risk of intrauterine infection (R^2 = 9.54, 95% CI: 3.52–25.85, P < 0.0004; and R^2 = 3.41, 95% CI: 1.05–11.13, P = 0.04, respectively).

Conclusion: Amniocentesis increases the risk of mother-to-child vertical transmission in pregnant women with HBV-DNA 10 copies/mL and/or HBeAg positivity.

Keywords: amniocentesis; mother-to-child transmission; chronic hepatitis B; HBV; meta-analysis

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Introduction

HBV infection is a serious global health problem, with 350–400 million people infected worldwide [1-2]. Approximately 600,000 deaths occur annually from liver-related complications such as acute liver failure, cirrhosis, and primary hepatocellular carcinoma [3]. China is a high-prevalence region for chronic HBV infection; the 2006 national epidemiological survey revealed an HBsAg carrier rate of 7.18% among the general population aged 1–59 years. China currently has about 93 million chronic HBV carriers, including approximately 20 million chronic hepatitis B (CHB) patients. Mother-to-child transmission accounts for 30–50% of chronic HBV infections, and the probability of becoming a chronic carrier increases with younger age at infection [4]. In Asian countries, perinatal or vertical transmission represents the most common route of HBV infection [5]. Therefore, blocking mother-to-child vertical transmission (MTCT) is one of the most effective measures to reduce new HBV infections.

The combined active-passive immunoprophylaxis using hepatitis B vaccine and HBIG effectively reduces MTCT, yet 5–10% of newborns still experience immunoprophylaxis failure due to intrauterine infection [6]. Amniocentesis, also known as amniotic fluid sampling, involves extracting amniotic fluid under ultrasound guidance. Amniotic fluid cells are shed fetal cells containing genetic information identical to the fetus. Typically performed at 14–20 weeks of gestation, it has become an indispensable tool in perinatal medicine with expanding applications, primarily for diagnosing fetal chromosomal abnormalities, inherited metabolic diseases, genetic molecular disorders, and congenital malformations [7-9]. This study aims to investigate whether amniocentesis increases the risk of intrauterine HBV infection in pregnant women with chronic hepatitis B or HBV carrier status, providing evidence for future clinical practice.

Methods

1.1 Search Strategy

Two investigators independently searched for relevant English and Chinese articles published between January 1, 1990, and March 15, 2016, in PubMed, Embase, Google Scholar, and Wanfang databases. Search terms included: "amniotic fluid/amniocentesis," "hepatitis B/hepatitis B virus," "intrauterine/prenatal," "mother-to-child transmission/MTCT blocking/vertical transmission," and "hepatitis B virus/HBV, Amniocentesis, vertical/mother-to-child transmission." Retrospective or prospective clinical studies were included, along with conference proceedings and dissertations [Figure 1: see original paper].

1.2 Inclusion and Exclusion Criteria

Inclusion Criteria:
(1) Pregnant women with persistent HBsAg positivity for >6 months, normal liver function, and no clinical symptoms or signs, who either underwent or did not undergo amniocentesis;
(2) No antiviral or immunotherapy during pregnancy;
(3) No pre-existing hypertension, diabetes, or heart disease, and no smoking or alcohol consumption history;
(4) Newborns received hepatitis B immunoglobulin and hepatitis B vaccine after birth;
(5) HBsAg detection by enzyme-linked immunosorbent assay (ELISA), with intrauterine transmission defined as positive HBsAg in neonatal peripheral venous blood persisting until 7 months postpartum .

Exclusion Criteria:
(1) No control group;
(2) Unclear intervention measures;
(3) Use of antiviral or other drugs (e.g., immunomodulators, cytotoxic agents) during pregnancy;
(4) Co-infection with other viruses (hepatitis A, C, D, E, HIV);
(5) Review articles;
(6) Pathology reports or epidemiological reports;
(7) Duplicate publications;
(8) Non-English/Chinese languages (e.g., Russian, Dutch).

1.3 Data Extraction and Quality Assessment

Two investigators independently screened titles and abstracts, then reviewed full texts to determine eligibility, perform quality assessment, and extract data. Disagreements were resolved through discussion. Extracted data included: first author, publication date, journal/volume/pages, study population, interventions and case numbers, control group numbers, and neonatal HBsAg positivity rates at birth, 6 months, and 1 year. Literature quality was evaluated using the Newcastle-Ottawa Scale (NOS), with high-quality articles scoring up to 9 points and a minimum of 5 points . Methodological quality was assessed using Cochrane Collaboration' s tool .

1.4 Statistical Analysis

Data from included articles were analyzed using Review Manager Version 5.0. The Mantel-Haenszel method was used for statistical testing. For heterogeneity analysis, a fixed-effects model was applied if no heterogeneity existed among studies ($P > 0.1$, I^2 50%); a random-effects model was used if heterogeneity was present ($P < 0.1$, $I^2 > 50\%$). Subgroup analysis was conducted if factors causing heterogeneity were identified. Statistical significance was defined as $P < 0.05$.

Results

Literature Inclusion

According to inclusion criteria, 28 articles were identified, and after excluding ineligible studies, four articles were included. Three articles collected neonatal peripheral venous blood for HBsAg testing at birth, and all four articles collected peripheral venous blood for HBsAg testing at 7 months to 5 years of age (Table 1). Basic characteristics of included cases are shown in Table 4 .

2.1 Analysis of Amniocentesis Impact on Infant HBsAg Positivity

Four articles met inclusion criteria, comprising 167 cases in the experimental group and 3,830 in the control group. Heterogeneity testing using RevMan software revealed no heterogeneity among studies ($I^2 = 0\%$, $P = 0.43$), so a fixed-effects model was applied. No significant difference in infant HBsAg positivity rates was found between amniocentesis and control groups ($R^2 = 1.37$, 95% CI: 0.70–2.69, $P = 0.36$) [Figure 2: see original paper].

2.2 Subgroup Analysis by Maternal HBV DNA Levels

Based on available data (94 amniocentesis cases vs. 271 controls), analysis showed that amniocentesis did not increase MTCT risk when maternal HBV-DNA was < 10 copies/mL ($P = 0.48$). However, amniocentesis significantly increased vertical transmission risk when maternal HBV-DNA 10 copies/mL ($R^2 = 9.54$, 95% CI: 3.52–25.85, $P < 0.0004$) [Figure 3: see original paper].

2.3 Subgroup Analysis by Maternal HBeAg Status

Among 36 HBeAg-positive women who underwent amniocentesis versus 145 controls, and 68 HBeAg-negative women who underwent amniocentesis versus 135 controls, analysis revealed no significant impact on MTCT for HBeAg-negative mothers ($P = 0.12$). However, HBeAg-positive mothers showed increased fetal HBV transmission risk ($R^2 = 3.41$, 95% CI: 1.05–11.13, $P = 0.04$) [Figure 4: see original paper].

Discussion

This meta-analysis found that amniocentesis in pregnant women with chronic hepatitis B or HBV carrier status increases fetal intrauterine HBV infection risk when serum HBV-DNA 10 copies/mL or HBeAg is positive. However, no statistically significant difference was observed for amniocentesis in the general HBV carrier population when maternal HBV-DNA < 10 copies/mL or HBeAg is negative.

Current active-passive immunoprophylaxis with hepatitis B vaccine and HBIG is highly effective for infants exposed to HBV at birth, administered as HBIG at birth and 1 month, and hepatitis B vaccine over 6 months [10-12]. Nevertheless, 10% of infants still experience prophylaxis failure [13-14]. Among 173 HBV-infected pregnant women undergoing amniocentesis, the MTCT rate was 7.14% at 6 months postpartum, comparable to previous studies [15]. In 1994, Grosheide et al. [16] performed amniocentesis in 17 HBsAg-positive pregnant women (including 2 HBeAg-positive), with no HBsAg-positive infants at birth, suggesting low MTCT risk but insufficient data on HBeAg impact. In 1999, Alexander et al. [17] similarly found no increased MTCT risk after amniocentesis.

Towers et al. [19] detected HBsAg in amniotic fluid but not HBV DNA in cord blood at delivery among 47 HBsAg-positive women undergoing amniocentesis, suggesting HBsAg can cross the placenta but transmitted viral particles may be incomplete, further indicating that amniocentesis does not transmit intact HBV DNA to the fetus. Another study found no correlation between maternal peripheral blood and amniotic fluid HBV DNA levels via logistic regression [20].

Amniocentesis approaches include transplacental and non-transplacental routes. While HBsAg and HBV DNA positivity rates appeared higher in transplacental samples (16 cases) versus non-transplacental samples (32 cases), the difference was not statistically significant [18]. Another study reached similar conclusions: 3 of 33 transplacental cases had positive amniotic fluid HBV DNA versus 3 of 65 non-transplacental cases ($P > 0.5$) [20].

In conclusion, while amniocentesis shows no significant statistical difference in MTCT risk across all HBV-infected pregnant women, the procedure increases MTCT risk when maternal HBV-DNA 10 copies/mL and/or HBeAg is positive. Therefore, for high-risk pregnant women, the benefits and risks of amniocentesis must be carefully weighed to reduce mother-to-child HBV transmission.

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