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Breastfeeding of Newborns by Mothers Carrying Hepatitis B Virus

A Meta-analysis and Systematic Review

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Objective: To perform a systematic review of prospective studies to confirm the role of breastfeeding in mother-to-child transmission (MTCT) of hepatitis B virus (HBV).

Data Sources: A database was constructed from MEDLINE, EMBASE, Cochrane Library, National Science Digital Library, and China Biological Medicine Database and through contact with experts in this field from January 1, 1990, to August 31, 2010.

Study Selection: All studies were peer reviewed and met the preset inclusion standards.

Main Exposure: Breastfeeding.

Main Outcome Measures: Data regarding HBV intrauterine infection, MTCT, maternal blood and breast milk infectiousness, infant immunoprophylaxis methods and response, and adverse events. The Mantel-Haenszel fixed-effects model was used for all analyses using odds ratios and 95% confidence intervals.

Results: Ten qualified studies were included. All were clinical controlled trials, involving 751 infants in the

breastfeeding group and 873 infants in the nonbreastfeeding group. As indicated by infant peripheral blood hepatitis B surface antigen or HBV DNA positivity at age 6 to 12 months, the odds ratio of MTCT of HBV in the breastfeeding group compared with that in the nonbreastfeeding group was 0.86 (95% confidence interval, 0.51-1.45) (from 8 clinical controlled trials, $P=.56$; $I^2=0\%$, $P=.99$). As indicated by infant peripheral blood hepatitis B surface antibody positivity at age 6 to 12 months, the odds ratio of development of hepatitis B surface antibodies in the breastfeeding group compared with that in the nonbreastfeeding group was 0.98 (95% confidence interval, 0.69-1.40) (from 8 clinical controlled trials, $P=.93$; $I^2=0\%$, $P=.99$). No adverse events or complications during breastfeeding were observed.

Conclusion: Breastfeeding after proper immunoprophylaxis did not contribute to MTCT transmission of HBV.

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ACCORDING TO THE WORLD Health Organization, more than 2 billion people worldwide have past or present serological evidence of hepatitis B virus (HBV) infection, and 350 million of them are chronic HBV carriers.¹ Approximately 40% to 50% of chronic carrier states are the result of mother-to-child transmission (MTCT),² including vertical (intrauterine transmission, transmission during labor, and breastfeeding) and horizontal (daily contact) transmission. Presently, the World Health Organization, the World Gastroenterology Organisation, and the Centers for Disease Control and Prevention recommend joint immunoprophylaxis using hepatitis B vaccine (HBVax) and hepatitis B immunoglobulin (HBIG) at birth to interrupt HBV transmission during and after deliv-

ery from HBV-carrying mothers to their newborns.³⁻⁵ However, these recommendations are aimed at the general HBV-carrying population, most of whom have very low HBV infectiousness (HBV DNA undetectable). Owing to the detection of HBV markers in the breast milk of highly infectious HBV-carrying mothers, there are still controversies concerning the possibility of HBV infection through breastfeeding.^{6,7} This meta-analysis evaluated the role of breastfeeding in HBV MTCT at 6 to 12 months after birth.

METHODS

SOURCES

We searched MEDLINE, EMBASE, Cochrane Library, National Science Digital Library, and China Biological Medicine Database for relevant prospective clinical controlled trials

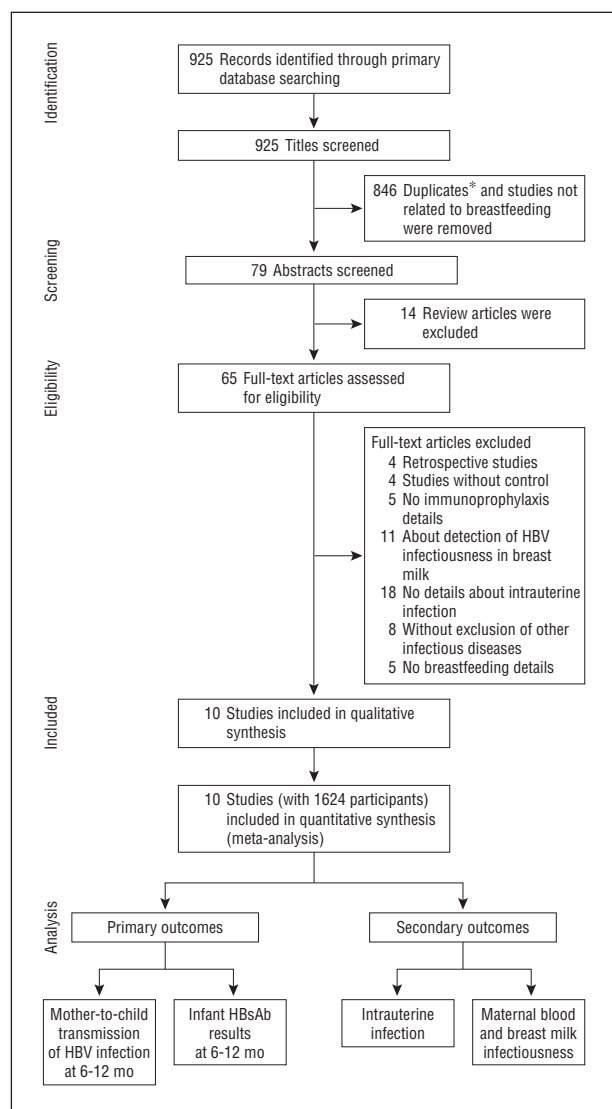


Figure 1. Flowchart of study selection and data extraction. Only prospective clinical controlled trials (CCTs) from peer-reviewed journals or conferences were included; CCTs that did not meet the criteria set in the search section were excluded, as were CCTs without enough information about patients' clinical conditions, baseline, treatment of newborns, or follow-up. Authors were further contacted if their names appeared more than once in the included CCTs to rule out duplicate publication of their work. *Cross-included in different database sources or publication in both English and Chinese languages. HBV indicates hepatitis B virus; HBsAb, hepatitis B surface antibody.

(CCTs) analyzing the risk of MTCT due to breastfeeding. Queries included articles published from January 1, 1990, to August 31, 2010, in English or Chinese peer-reviewed publications (including abstracts). Keywords were "breastfeeding" (or "breast feeding" or "breastfed") and "HBV" (or "hepatitis B virus"). We also hand-searched bibliographies of original studies, reviews (including meta-analyses), and relevant conference abstracts and contacted some investigators directly. The date last searched was September 15, 2010. All newborns (in both breastfeeding and nonbreastfeeding groups) received the schedule of HBIG and/or HBVac immunoprophylaxis beginning within 24 hours after birth as recommended by the World Health Organization.³

STUDY SELECTION

Two of us (Y.Y. and H.W.) independently selected relevant studies, extracted data, and assessed trial quality. Questionable stud-

ies were confirmed or rejected by discussion with a third person (L.M.). Inclusion criteria included the following: descriptions of HBV intrauterine infection, MTCT, newborn joint immunoprophylaxis, breastfeeding (>1 month), and follow-up results (after completion of the immunoprophylaxis schedule) were clear; and mothers in included studies were all hepatitis B surface antigen (HBsAg) seropositive and asymptomatic, had no other infectious diseases or complications (such as human immunodeficiency virus coinfection or severe liver or kidney disease), and were not taking other immunosuppressive medications during pregnancy (**Figure 1**). Breastfeeding should have been paused when there were cracked or bleeding nipples or lesions with serous exudates until they recovered. We abstracted data about study design and methods, inclusion and exclusion criteria, clinical characteristics of participants, intrauterine and in-delivery infection, breastfeeding duration and outcomes (MTCT and production of hepatitis B surface antibody [HBsAb] in response to immunoprophylaxis), and adverse events.

For primary outcomes, we estimated the rate of HBV MTCT and production of HBsAb in response to immunoprophylaxis in infants (the observed proportion) at age 6 to 12 months. Secondary outcomes included HBV intrauterine and in-delivery infection, maternal blood and breast milk HBV markers at the beginning of breastfeeding, and adverse events in both mothers (such as transaminase level increase, intolerance to breastfeeding) and their newborns (such as incompatibility to breastfeeding). In the included CCTs, the diagnosis of HBV intrauterine infection and MTCT were defined as neonatal peripheral blood (collected from the femoral artery) HBsAg or HBV DNA positivity at birth and at age 6 to 12 months (collected from the ulnar vein), respectively.

Statistical analyses were conducted using Review Manager version 5.0 software (Cochrane Collaboration, Oxford, England). Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were determined by choice between the Mantel-Haenszel fixed-effects model and random-effects model, whichever was most conservative (showing less efficacy and a higher *P* value; the fixed-effects model qualified for this purpose) and shown in forest plot. Statistical between-study heterogeneity was assessed by *I*² test and χ^2 test. Publication bias was assessed by funnel plot. For all tests, statistical significance was achieved if *P* < .05 (for overall effect of intervention) or *P* < .10 (for heterogeneity test).⁸

RESULTS

Ten qualified studies⁹⁻¹⁸ were included, all of which were CCTs performed in China. Eight CCTs investigated the role of breastfeeding in MTCT of HBV after joint immunoprophylaxis with HBIG and HBVac in newborns and 3 CCTs examined the same objective after immunization of newborns with only HBVac (**Table** and **Figure 1**), including 751 infants in the breastfeeding group and 873 infants in the nonbreastfeeding group. According to diagnosis criteria, MTCT of HBV, production of HBsAb, and intrauterine infection (**Figures 2, 3, and 4** according to newborn or infant HBsAg, HBV DNA, or HBsAb seropositivity) as well as maternal blood infectiousness (shown by hepatitis B e antigen [HBeAg] or HBV DNA) (**Figure 5**) and breast milk infectiousness (**Figure 6**) were evaluated for comparison purposes. Funnel plots indicating selection bias were also shown in the corresponding comparisons.

Table. Clinical Characteristics of Participants and Interventions of Included Studies

Source	Follow-up, mo	Infant IP ^a	Maternal Blood ^b		Breast Milk ^b		Newborn ^b			Infant ^b		
			HBeAg	HBV DNA	HBsAg	HBV DNA	HBsAg	HBV DNA	HBsAb	HBsAg	HBV DNA	HBsAb
Wang et al, ⁹ 2003	12	HBIG (100 IU at birth) and HBVac (5 µg at birth, 1 mo, 6 mo)	12/33:46/135	NA	NA	NA	4/33:14/135	NA	NA	0/33:4/135	NA	30/33:122/135
Wang et al, ⁹ 2003	12	HBVac (5 µg at birth, 1 mo, 6 mo)	7/21:13/41	NA	NA	NA	2/21:5/41	NA	NA	1/21:3/41	NA	17/21:30/41
Meng et al, ¹⁰ 2004	6	HBVac (5 µg at birth, 1 mo, 6 mo)	NA	NA	20/55:37/79 57+	NA	9/55:13/79 4/20:6/37	1/55:2/79 0/20:1/37	27/55:36/79 10/20:16/37	1/55:2/79 0/20:1/37	1/55:2/79 0/20:1/37	46/55:67/79 16/20:31/37
Mou et al, ¹¹ 2005	12	HBIG (200 IU at birth, 2 wk) and HBVac (5 µg at birth, 1 mo, 6 mo)	18/55:12/36	19/55:15/36	NA	NA	NA	7/55:5/36	NA	NA	5/55:3/36	50/55:33/36
Chen, ¹² 2006	12	HBIG (200 IU at birth, 2 wk) and HBVac (5 µg at birth, 1 mo, 6 mo)	52/122:18/48	48/122:19/48	NA	NA	NA	11/122:5/48	NA	NA	9/122:4/48	117/122:45/48
He et al, ¹³ 2006	6	HBVac (10 µg at birth, 1 mo, 6 mo)	NA	NA	85+ 38 ^c	NA	8/38:9/47 5/10:5/28	NA	9/38:16/47 1/10:12/28	4/38:4/47 2/10:3/28	NA	27/38:38/47 7/10:19/28
Zeng et al, ¹⁴ 2006	7	HBIG (200 IU at birth, 4 wk) and HBVac (5 µg at 3 d, 1 mo, 6 mo)	22/70:14/45	NA	24/70:18/45	35/70:25/45	8/70:6/45	NA	NA	4/70:4/45	NA	60/70:38/45
Wang et al, ¹⁵ 2007	12	HBIG (200 IU at birth) and HBVac (5 µg at birth, 1 mo, 6 mo)	–	NA	NA	NA	8/64:11/101	NA	12/64:19/101	2/64:5/101	NA	58/64:91/101
Liu et al, ¹⁶ 2010	12	HBIG (200 IU at 2 d, 1 mo, 3 mo) and HBVac (5 µg at birth, 1 mo, 6 mo)	NA	36/61:39/68	29/61:30/68	24/61:25/68	6/61:7/68	3/61:3/68	7/61:9/68	3/61:4/68	2/61:2/68	55/61:61/68
Liu and Liu, ¹⁷ 2010	12	HBIG (200 IU at birth, 2 wk) and HBVac (5 µg at birth, 1 mo, 6 mo)	NA	NA	NA	NA	17/195:21/241	NA	NA	8/195:9/241	NA	164/195:209/241
Sun et al, ¹⁸ 2010	12	HBIG (200 IU at birth) and HBVac (5 µg at birth, 1 mo, 6 mo)	NA	NA	NA	–	NA	–	NA	0/37:0/32	NA	32/37:26/32

Abbreviations: HBeAg, hepatitis B e antigen; HBIG, hepatitis B immunoglobulin; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HBVac, hepatitis B vaccine; IP, immunoprophylaxis; NA, not available; +, positive participants; –, negative participants.

^aThe HBVac used was of yeast cell origin.

^bRatios are number of positive participants/total number of participants in the breastfeeding group:nonbreastfeeding group. When both HBeAg and HBV DNA data (to determine the infectiousness of maternal blood or breast milk) or both HBsAg and HBV DNA data (to determine in utero transmission or mother-to-child transmission) were available, the numbers in bold, which showed a higher percentage of HBV positivity, were used for analysis. The italicized ratios showed a possibility of false positivity or HBV mutants that were resistant to the HBVac.

^cPositive for HBsAg and HBeAg in breast milk.

PRIMARY OUTCOMES

Breastfeeding vs Nonbreastfeeding in MTCT of HBV at Age 6 to 12 Months

The effect of breastfeeding vs nonbreastfeeding in MTCT of HBV was shown in 2 categories. In infants

who received HBIG and HBVac joint immunoprophylaxis, there were 31 positive cases of MTCT of HBV among 637 total participants in the breastfeeding group compared with 33 cases among 706 participants in the nonbreastfeeding group (indicated by infant peripheral blood HBsAg or HBV DNA), with the pooled OR being 0.86 (95% CI, 0.51-1.45) (8 CCTs, $P=.56$; with mini-

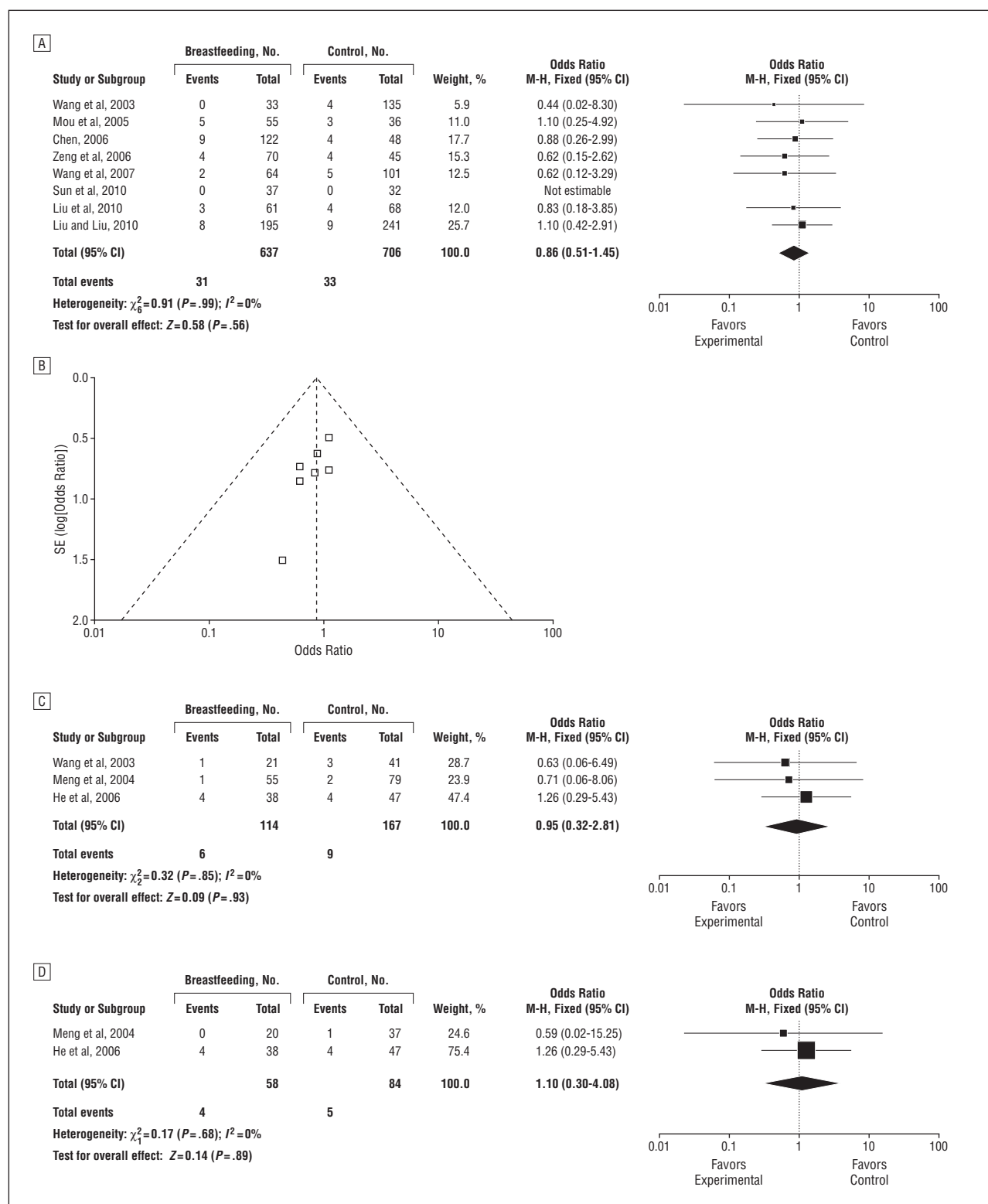


Figure 2. Breastfeeding vs nonbreastfeeding in mother-to-child transmission of hepatitis B virus, showing infants after hepatitis B immunoglobulin and hepatitis B vaccine joint immunoprophylaxis (A) and the corresponding funnel plot (B), infants after only hepatitis B vaccine immunoprophylaxis (C), and infants after only hepatitis B vaccine immunoprophylaxis who were fed with infectious breast milk (D). A, C, and D, Vertical lines indicate no difference between compared interventions; horizontal lines, 95% confidence intervals (CIs); squares, point estimates; size of squares, weight of each study in the meta-analysis; and M-H, Mantel-Haenszel test. Studies and subgroups are as follows: Wang et al,⁹ 2003; Mou et al,¹¹ 2005; Chen,¹² 2006; Zeng et al,¹⁴ 2006; Wang et al,¹⁵ 2007; Sun et al,¹⁸ 2010; Liu et al,¹⁶ 2010; Liu and Liu,¹⁷ 2010; Meng et al,¹⁰ 2004; and He et al,¹³ 2006.

mum heterogeneity, $I^2=0\%$, $P=.99$). In infants who received only HBV vaccine immunoprophylaxis, 6 of 114 participants in the breastfeeding group and 9 of 167

participants in the nonbreastfeeding group had MTCT of HBV, with the OR being 0.95 (95% CI, 0.32-2.81) (3 CCTs, $P=.93$; $I^2=0\%$, $P=.85$). In infants who received

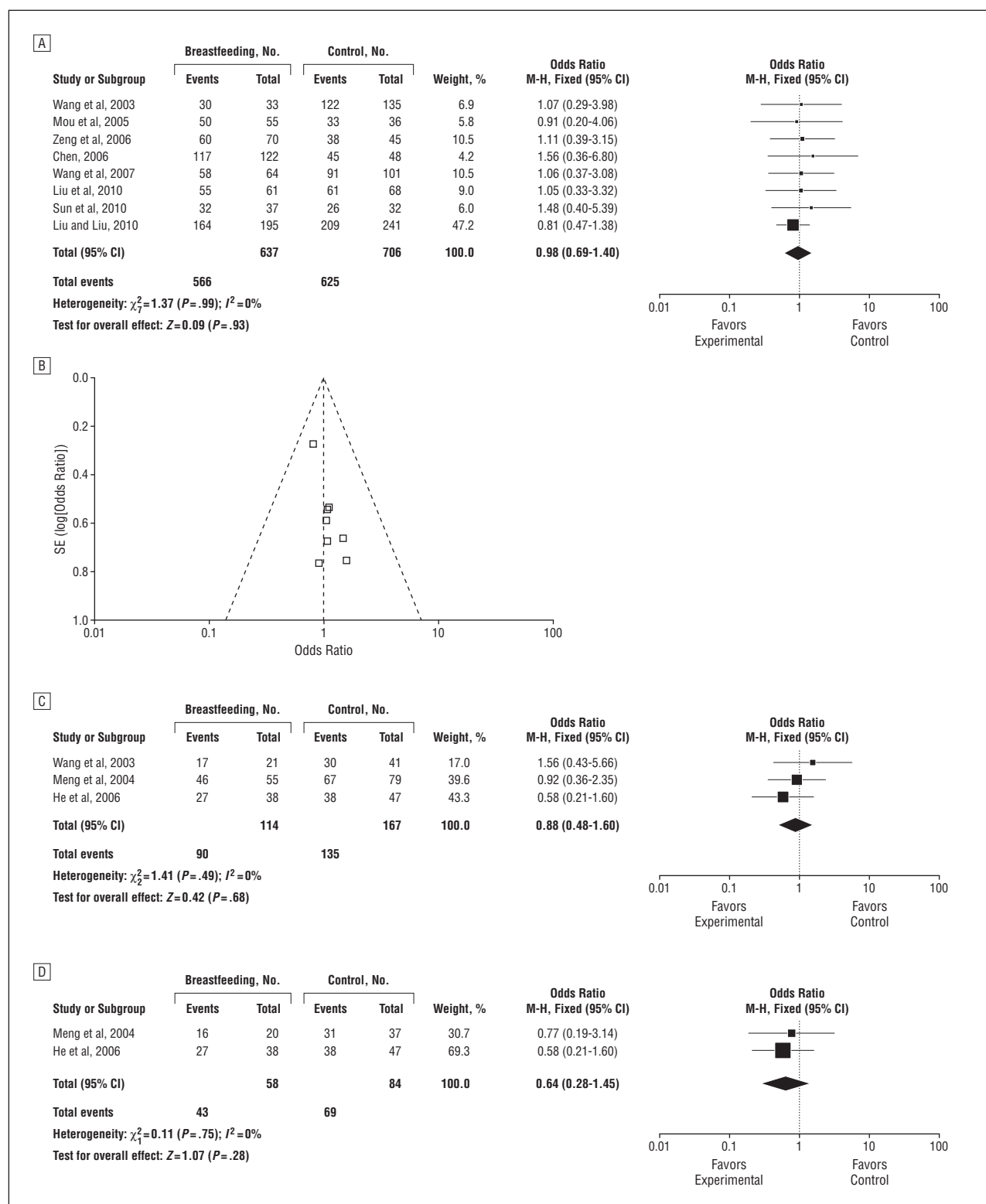


Figure 3. Breastfeeding vs nonbreastfeeding in production of hepatitis B surface antibody in infants after hepatitis B immunoglobulin and hepatitis B vaccine joint immunoprophylaxis (A) and the corresponding funnel plot (B), infants after only hepatitis B vaccine immunoprophylaxis (C), and infants after only hepatitis B vaccine immunoprophylaxis who were fed with infectious breast milk (D). A, C, and D. Vertical lines indicate no difference between compared interventions; horizontal lines, 95% confidence intervals (CIs); squares, point estimates; size of squares, weight of each study in the meta-analysis; and M-H, Mantel-Haenszel test. Studies and subgroups are as follows: Wang et al,⁹ 2003; Mou et al,¹¹ 2005; Zeng et al,¹⁴ 2006; Chen,¹² 2006; Wang et al,¹⁵ 2007; Liu et al,¹⁶ 2010; Sun et al,¹⁸ 2010; Liu and Liu,¹⁷ 2010; Meng et al,¹⁰ 2004; and He et al,¹³ 2006.

only HBVac immunoprophylaxis and were fed with infectious breast milk (HBsAg or HBV DNA detected in

breast milk), the OR was 1.10 (95% CI, 0.30-4.08) (2 CCTs, $P = .89$; $I^2 = 0\%$, $P = .68$) (Figure 2).

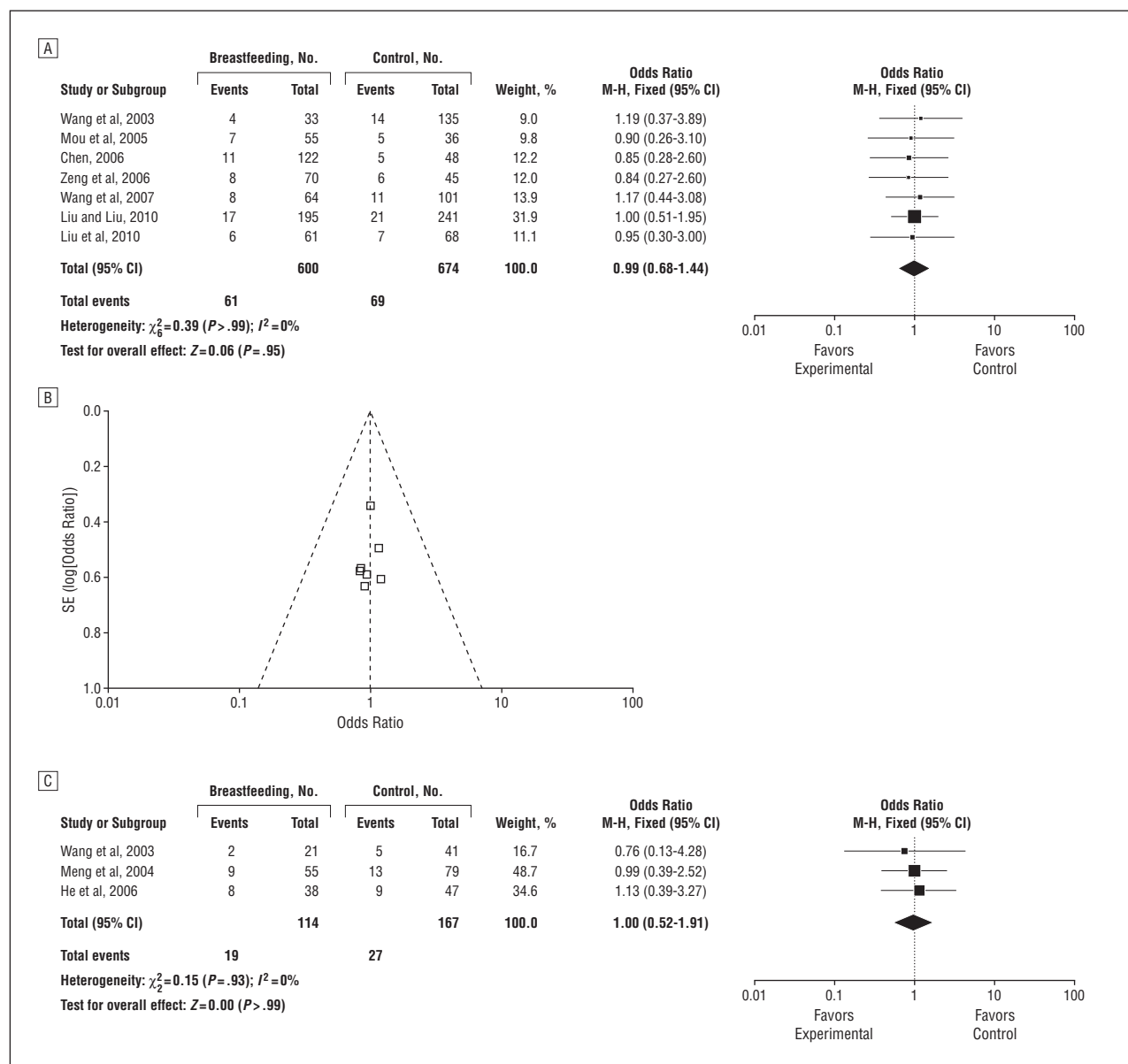


Figure 4. Incidence of intrauterine infection and infection during delivery in breastfeeding and nonbreastfeeding groups in infants who followed hepatitis B immunoglobulin and hepatitis B vaccine joint immunoprophylaxis (A) and the corresponding funnel plot (B) as well as infants who followed only hepatitis B vaccine immunoprophylaxis (C). A and C, Vertical lines indicate no difference between compared interventions; horizontal lines, 95% confidence intervals (CIs); squares, point estimates; size of squares, weight of each study in the meta-analysis; and M-H, Mantel-Haenszel test. Studies and subgroups are as follows: Wang et al,⁹ 2003; Mou et al,¹¹ 2005; Chen,¹² 2006; Zeng et al,¹⁴ 2006; Wang et al,¹⁵ 2007; Liu and Liu,¹⁷ 2010; Liu et al,¹⁶ 2010; Meng et al,¹⁰ 2004; and He et al,¹³ 2006.

Breastfeeding vs Nonbreastfeeding in Production of HBsAb at Age 6 to 12 Months

The effect of breastfeeding vs nonbreastfeeding in response to immunoprophylaxis was also shown in 2 categories. In infants who received HBIG and HBVac joint immunoprophylaxis, there were 566 cases of HBsAb positivity among 637 participants in the breastfeeding group compared with 625 cases among 706 participants in the nonbreastfeeding group (indicated by infant peripheral blood HBsAb), with the pooled OR being 0.98 (95% CI, 0.69-1.40) (8 CCTs, $P = .93$; with minimum heterogeneity, $I^2 = 0\%$, $P = .99$). In infants who received only HBVac immunoprophylaxis, there were 90 cases of HBsAb positivity among 114 participants in the breast-

feeding group and 135 cases among 167 participants in the nonbreastfeeding group, with the OR being 0.88 (95% CI, 0.48-1.60) (3 CCTs, $P = .68$; $I^2 = 0\%$, $P = .49$). In infants who received only HBVac immunoprophylaxis and were fed with infectious breast milk, the OR was 0.64 (95% CI, 0.28-1.45) (2 CCTs, $P = .28$; $I^2 = 0\%$, $P = .75$) (Figure 3).

SECONDARY OUTCOMES

Incidence of HBV Transmission in Pregnancy and Delivery

To minimize the influence of intrauterine infection or transmission during delivery on the final result of MTCT due to breastfeeding, the newborns' serum-positive rate of HBsAg

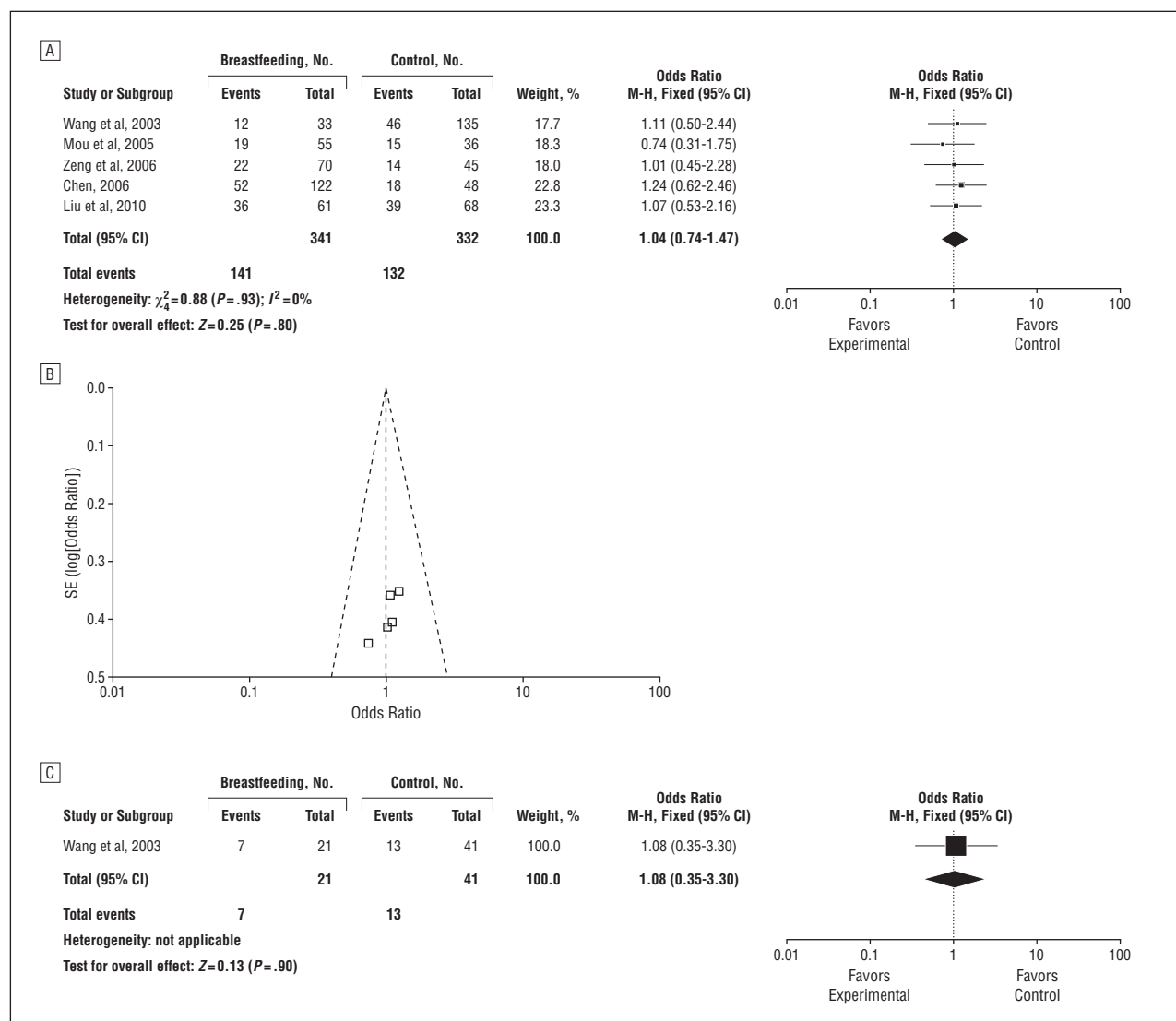


Figure 5. Maternal blood infectiousness in breastfeeding vs nonbreastfeeding groups in infants who followed hepatitis B immunoglobulin and hepatitis B vaccine joint immunoprophylaxis (A) and the corresponding funnel plot (B) as well as infants who followed only hepatitis B vaccine immunoprophylaxis (C). A and C, Vertical lines indicate no difference between compared interventions; horizontal lines, 95% confidence intervals (CIs); squares, point estimates; size of squares, weight of each study in the meta-analysis; and M-H, Mantel-Haenszel test. Studies and subgroups are as follows: Wang et al,⁹ 2003; Mou et al,¹¹ 2005; Zeng et al,¹⁴ 2006; Chen,¹² 2006; and Liu et al,¹⁶ 2010.

or HBV DNA at birth was analyzed. In infants who received HBIG and HBVac joint immunoprophylaxis, 61 of 600 newborns had HBsAg or HBV DNA positivity before breastfeeding in the breastfeeding group compared with 69 of 674 newborns in the nonbreastfeeding group, with the pooled OR being 0.99 (95% CI, 0.68-1.44) (7 CCTs, $P = .95$; with minimum heterogeneity, $I^2 = 0\%$, $P > .99$). In infants who received only HBVac immunoprophylaxis, 19 of 114 newborns in the breastfeeding group and 27 of 167 newborns in the nonbreastfeeding group had HBsAg or HBV DNA positivity, with the OR being 1.00 (95% CI, 0.52-1.91) (3 CCTs, $P > .99$; $I^2 = 0\%$, $P = .93$) (Figure 4).

Infectiousness of Maternal Blood and Breast Milk

The influence of infectiousness of maternal blood and breast milk on the final result of MTCT due to breast-

feeding was analyzed. Five CCTs studied the infectiousness of maternal blood (shown by HBeAg or HBV DNA positivity) in infants who received HBIG and HBVac joint immunoprophylaxis in the breastfeeding group (141 of 341 infants) vs the nonbreastfeeding group (132 of 332 infants), with the pooled OR being 1.04 (95% CI, 0.74-1.47) ($P = .80$; with minimum heterogeneity, $I^2 = 0\%$, $P = .93$). In infants who received only HBVac immunoprophylaxis, 7 of 21 infants in the breastfeeding group and 13 of 41 infants in the nonbreastfeeding group had HBsAg or HBV DNA positivity from maternal blood, with the OR being 1.08 (95% CI, 0.35-3.30) (1 CCT, $P = .90$) (Figure 5). Two CCTs studied the infectiousness of breast milk (shown by HBsAg or HBV DNA positivity) in infants who received HBIG and HBVac joint immunoprophylaxis in the breastfeeding group (64 of 131 infants) vs the nonbreastfeeding group (55 of 113 infants), with the pooled OR being 0.97 (95% CI, 0.58-1.62) ($P = .91$;

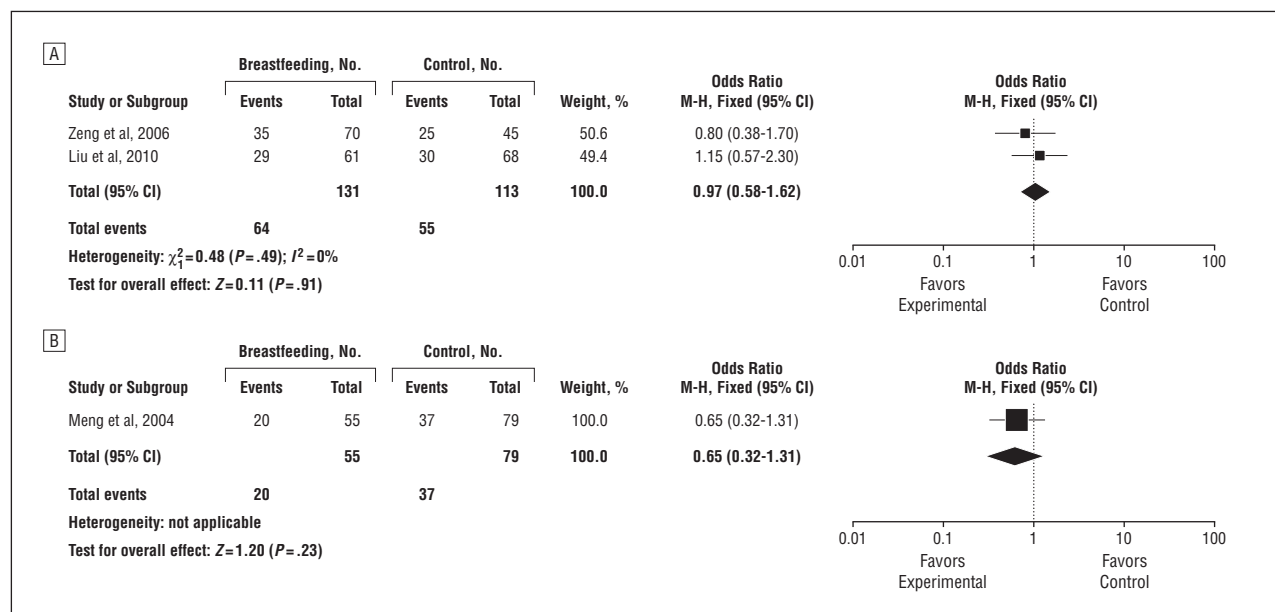


Figure 6. Breast milk infectiousness in breastfeeding vs nonbreastfeeding groups in infants who followed hepatitis B immunoglobulin and hepatitis B vaccine joint immunoprophylaxis (A) as well as infants who followed only hepatitis B vaccine immunoprophylaxis (B). Vertical lines indicate no difference between compared interventions; horizontal lines, 95% confidence intervals (CIs); squares, point estimates; size of squares, weight of each study in the meta-analysis; and M-H, Mantel-Haenszel test. Studies and subgroups are as follows: Zeng et al,¹⁴ 2006; Liu et al,¹⁶ 2010; and Meng et al,¹⁰ 2004.

with minimum heterogeneity, $I^2=0\%$, $P=.49$). In infants who received only HBV vaccine immunoprophylaxis, 20 of 55 infants in the breastfeeding group and 37 of 79 infants in the nonbreastfeeding group had HBsAg or HBV DNA positivity from breast milk, with the OR being 0.65 (95% CI, 0.32-1.31) (1 CCT, $P=.23$) (Figure 6). There was no report of adverse effects during the process of breastfeeding.

COMMENT

Breast milk is a valuable source of nutrition for infants in general, but in the case of HBV-carrying mothers, the benefit of breastfeeding must be carefully weighed against the risk of transmission of HBV. Based on the results of 2 studies,^{19,20} the World Health Organization recommended breastfeeding by HBV-carrying mothers, reasoning that the “risk of transmission associated with breast milk is negligible compared to the high risk of exposure to maternal blood and body fluids at birth, and hepatitis B vaccination will substantially reduce perinatal transmission and virtually eliminate any risk of transmission through breastfeeding or breast milk feeding.”²¹ However, it was also stated that “experts on hepatitis did have concerns that breast pathology such as cracked or bleeding nipples or lesions with serous exudates could expose the infant to infectious doses of HBV.”²¹ Compared with infection during delivery, which is transient and after which the HBV that has entered the neonatal peripheral circulation during the delivery process can be neutralized by the injection of HBIG immediately after delivery, the large amount of breast milk (on average, dozens to hundreds of milliliters per day) in contrast to the immature gastric digestive function and fragile intestine membrane poses continuous risks for HBV transmission. Second, this recommendation was made in 1996,

when the test of infectiousness of maternal blood and breast milk by HBV quantitative polymerase chain reaction²² was not available. It has been reported that colostrum collected within 24 hours from the beginning of breast milk secretion is more infectious (shown by detectable HBV markers). Therefore, breastfeeding needs to be reevaluated to a more detailed extent.

Tang and Xiao²³ performed a meta-analysis that showed a positive correlation between breastfeeding and MTCT of HBV. However, there was no consideration of intra-uterine transmission, transmission during delivery, and schedule of immunoprophylaxis after birth. Hence, the result seems to be unconvincing owing to the involvement of MTCT during pregnancy and delivery.

Some studies reported HBV infection as HBsAg and HBV DNA positivity separately, while others summarized them together. Because this study aimed to analyze the risk of breastfeeding in MTCT of HBV, we applied the higher rate when both were available to minimize the influence of intrauterine transmission and transmission during delivery on the outcome of MTCT through breastfeeding.

Hepatitis B immunoglobulin contains high levels of exogenous antibody to HBsAg. This antibody can bind HBsAg, activate the complement system, and facilitate humoral immunity, providing protection for several weeks. Hepatitis B vaccine is made of recombinant HBsAg to induce endogenous HBsAb, which lasts several years. After implementing joint immunoprophylaxis with HBIG and HBV vaccine in the newborn to interrupt HBV MTCT, only 5% to 10% of newborns of HBsAg- and HBeAg-double seropositive mothers were unprotected.²⁴ Because most HBV infection in infants occurs within the first year of life²⁵ and the immunoprophylaxis schedules are finished by 6 to 7 months after birth, all studies tested peripheral serum of these infants at age 6 to 12 months to

determine the results of HBV MTCT and the efficacy of immunoprophylaxis. Hepatitis B immunoglobulin was used during pregnancy in some studies to interrupt in utero transmission of HBV,^{10,13,15,16} leading to the detection of HBsAb in the neonates at birth. It has been shown by our previous studies that giving HBIG or lamivudine to HBV-carrying mothers during late pregnancy may reduce the rate of intrauterine transmission of HBV.²⁶⁻²⁹ It should also be noted that most infants with MTCT of HBV diagnosed 6 to 12 months after following strict immunoprophylaxis schedules were already infected during pregnancy or delivery.

The rate of infected babies in our study (about 5%) is quite high compared with other studies in Western countries, where the incidence of failure of the prophylactic procedure is about 0.7%.³⁰ However, we should note that data in our study originated from China, where the HBV carrier rate is higher and maternal HBV infectiousness (shown by HBV DNA quantitation) is higher. Other possible causes might be transient HBV infections,³⁰ failure to comply with the correct immunoprophylaxis procedure,³¹ and inability of the test to detect all HBsAg or HBV DNA owing to a small number of copies or mutation of the virus.³² Because maternal serum and breast milk infectiousness are important factors in HBV MTCT, they were also evaluated in some included studies. Ngui et al³³ showed that intrauterine infection rates were higher when maternal HBV DNA was greater than 10⁸ copies/mL. In our analysis, there were no differences in maternal blood or breast milk HBV infectiousness between the breastfeeding and nonbreastfeeding groups.

Apparently, we included only CCTs published after 2002 in China. This was the strict enforcement result of our preset selection criteria. For example, Hill et al³⁴ carried out a prospective longitudinal study whose results suggested that breastfeeding poses no additional risk for HBV transmission. The study, although well designed and having results in concert with our present meta-analysis, was not included in our analysis because it did not describe the incidence of intrauterine infection with HBV. Although randomized controlled trials are more convincing and popular, they are not practical in the case of breastfeeding. It would be unethical to randomly allocate infants to the breastfeeding group or nonbreastfeeding group with the knowledge of infectious breast milk (HBV DNA positive). It is also not feasible to fulfill double blinding because breastfeeding itself involves the acknowledgment and activity of the mother. The inclusion of prospective CCTs is therefore proper under these circumstances. We searched only for studies published in English or Chinese, which might also render selection bias. In our analysis, the estimated OR is likely biased in favor of the intervention group due to publication bias. To more thoroughly evaluate the role of breastfeeding in HBV MTCT, more randomized controlled trials or CCTs with detailed breast milk HBV marker testing and larger size are needed for further investigations and more convincing results.

In summary, our meta-analysis provides strong evidence that without cracked or bleeding nipples or lesions, breastfeeding did not contribute to MTCT of HBV after proper immunoprophylaxis in the infants

and should be recommended as a valuable source of nutrition to infants.

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Author Contributions: Drs Shi, Y. Yang, Wang, and Ma contributed equally to this work. *Study concept and design:* Shi, Y. Yang, Wang, Ma, and Li. *Acquisition of data:* Shi, Y. Yang, Wang, Ma, Schreiber, Sun, Zhao, X. Yang, Zhang, Lu, Teng, and An. *Analysis and interpretation of data:* Shi, Y. Yang, Wang, and Ma. *Drafting of the manuscript:* Shi, Y. Yang, Wang, and Ma. *Critical revision of the manuscript for important intellectual content:* Schreiber, Li, Sun, Zhao, X. Yang, Zhang, Lu, Teng, and An. *Statistical analysis:* Shi. *Administrative, technical, and material support:* Y. Yang, Wang, Ma, Schreiber, Sun, Zhao, X. Yang, Zhang, Lu, Teng, and An. *Study supervision:* Li.

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