The Cochrane Collaboration methodology was applied to search PubMed, EMBASE, LILACS, BIOSIS and the Cochrane databases for articles in English, Portuguese, French or Spanish from 1988 to 2013. In addition, references of relevant articles and abstracts from major conferences were manually searched. The following search terms were used as both keywords and medical subject heading terms, where applicable, after consultation with a reference librarian (Paul Bain).
The primary meta-estimate – the OR of HBV transmission in Caesarean section compared with vaginal delivery – was calculated for all studies including 95% CIs. Meta-analyses using both fixed-effects (11) and a random-effects models were conducted (12). It was anticipated that there would be high level of heterogeneity among the studies; results were reported using the random-effects model. Binary outcomes are presented as OR with 95% CI. Pooled ORs and 95% CI were determined using a Mantel-Haenszel random-effects model. An OR of <1 favoured Caesarean section as having a preventive effect on HBV transmission while an OR of >1 indicated that Caesarean section was harmful and increased HBV transmission. The point estimate of the OR was considered to be statistically significant at the P<0.05 level if the 95% CI did not include the value 1.

Statistical between-study heterogeneity was assessed using the I2 test to measure the extent of inconsistency among the results and p2 test, with statistical significance set at P<0.05. Publication bias was assessed using funnel plot (13). An asymmetric funnel plot suggests publication bias or a systematic difference between smaller and larger studies ('small study effects') or the use of an inappropriate effect measure. Publication bias was also evaluated by the Duval and Tweedie trim-and-fill method (14). To evaluate the impact of each individual study, sensitivity analyses using a one-study-removed method were performed. Temporal trends and secular changes were assessed with the cumulative analysis approach.

Because HBV transmission rates are directly influenced by prophylaxis with HBIG and vaccination, subgroup analyses were performed in an attempt to explain possible sources of heterogeneity and used the test for interaction ($\chi^2$ statistic) to estimate differences between groups. Unrestricted maximum likelihood random effects meta-regression was applied to percentage of HBIG administered as a continuous variable to evaluate for the impact of HBIG on HBV transmission rates. For all tests, a two-tailed P<0.05 was considered to be statistically significant. All analyses were performed in Comprehensive Meta Analysis Version 2.0 (Biostat, USA). The study is reported according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group reporting guidelines (15). All authors had access to the study data, and reviewed and approved the final manuscript.

RESULTS

Study selection

The search strategy identified 430 articles, of which 420 were excluded and 10 were included for analysis (Figure 1). Of the 10 studies included, eight were full-text articles (6, 7, 16-21) and two were major society meeting abstracts (9, 22). One abstract (22) was found in EMBASE. The other abstract (9) was identified by searching the reference lists of the retrieved full-text articles.

Study characteristics are described in Table 1. Nine studies were retrospective cohort studies and one was a case-control study. The primary meta-estimate measured was the OR of HBV transmission from mothers to newborns among women who underwent Caesarean section (n = 2352) compared with vaginal delivery (n = 2739), yielding a total of 5091 newborns. The HBV transmission rate was 8% overall: 5% (116 of 2352) for mothers who underwent Caesarean section and 10% (283 of 2739) for those who underwent vaginal delivery. Three studies were conducted in HBsAg+ women exclusively, one study did not specify, and the remaining studies had mixed HBsAg+ and negative populations (range 25% to 55% HBsAg+). Prophylaxis rates with HBIG and HBV vaccination of infants varied across studies: three reported 100% prophylaxis with HBIG and vaccination, one did not mention prophylaxis rate, and the remaining studies reported a wide range (HBIG 51% to 76%, vaccination 1% to 100%). Four studies differentiated urgent from elective Caesarean section; only one study described whether instrumentation (forceps or suction) was used during delivery. Only four studies explicitly stated their exclusion criteria; all four excluded HIV, three excluded HCV coinfection and three excluded any form of recent HBV therapy (nucleos(t)ide analogues or...
Meta-analysis

Seven studies demonstrated decreased odds of HBV transmission, of which three were statistically significant, while three demonstrated increased odds of HBV transmission, but none were statistically significant (Figure 2). The overall meta-analysis demonstrated a statistically significant decrease in HBV vertical transmission with Caesarean section compared with vaginal delivery, with an OR of 0.62 (95% CI [0.40 to 0.978]; P=0.04). As expected, there was significant heterogeneity among the studies (Q test 25.58; P=0.003; I²=63%).

A one-study-removed analysis was generally consistent with the overall finding that Caesarean section was associated with a reduction in HBV transmission, although this resulted in having the upper limit of the 95% CI cross 1 (null) in seven of 10 cases (Wang et al [20] [OR 0.57 [95% CI 0.35 to 0.93], Chen et al [16] [OR 0.57 [95% CI 0.35 to 0.92] and Hu et al [6] [OR 0.55 [95% CI 0.36 to 0.83], forest plot not shown). A cumulative analysis demonstrated a persistent trend toward a protective effect of Caesarean section on HBV transmission as studies were added to the model over time, but this did not consistently reach statistical significance (data not shown). This finding may have been due to the publication of five studies in the same year. When including only high-quality studies (NOS ≥6) and excluding Chen et al [16] (NOS 4), Caesarean section still reduced HBV transmission (OR 0.57 [95% CI 0.35 to 0.83]). However, this effect was no longer statistically significant since the analysis to cohort studies (excluding Hu et al [6]) which was a case control study) (OR 0.70 [95% CI 0.44 to 1.11] or when considering only high-quality cohort studies (excluding both Chen et al [16] and Guo et al [18]) (OR 0.635 [95% CI 0.38 to 1.07]) (forest plots not shown).

A funnel plot was only mildly asymmetric, suggesting that smaller studies at the right margin of the plot, favouring an increase in HBV transmission with Caesarean section, may be missing (Figure 3). The Duval and Tweedie trim-and-fill method (14) did not add any studies, indicating that publication bias was not a significant factor.

Of the studies with <100% of HBIG administration in infants, the study by Hu et al (6) collected HBV prophylaxis administration data primarily using surveys one to seven years after childbirth, rendering the study vulnerable to recall bias. Additionally, the HBV transmission rate in the vaginal delivery group was disproportionately lower than expected (2%). While this may, in part, be due to the low HBeAg+ prevalence of 25%, the HBV transmission rate was still lower than Wen et al (21), which had a similar HBeAg+ prevalence of 27%, but a much higher HBV transmission rate of 4% in the vaginal delivery group, suggesting that the population in Hu et al (6) study may be fundamentally different from the other study populations. To better account for this persistent heterogeneity, a meta-regression was performed to evaluate a potential linear relationship between the percentage of patients administered HBIG and the log OR of HBV transmission. While there was no association in the initial model (P=0.78 [model not shown]), a subsequent meta-regression excluding Hu et al (6) (Figure 4) revealed a significant linear relationship, such that the log OR increased by 0.02 times for each percentage point increase in HBIG administered (P=0.005). This confirmed the expected clinical finding that HBV transmission decreased as HBIG use approached 100%, accounting for the underlying heterogeneity among studies.
<table>
<thead>
<tr>
<th>Author (reference), year (country)</th>
<th>Study design</th>
<th>Quality score</th>
<th>Exclusion criteria</th>
<th>Newborns by Caesarean/vaginal, n/n</th>
<th>HBV+ newborns by Caesarean/vaginal n/n</th>
<th>HBeAg+/&gt;10^6 copies/mL, %</th>
<th>Given HBIG vaccine, %</th>
<th>HBIG dosing</th>
<th>Vaccine schedule</th>
<th>Follow-up</th>
<th>Caesarean section, %</th>
<th>Forceps or vacuum, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al (19), 1988 (China)</td>
<td>Retrospective cohort</td>
<td>6/9</td>
<td>Not reported</td>
<td>62/385</td>
<td>6/96</td>
<td>100/-</td>
<td>76/100</td>
<td>50 IU ≤9 h at 1 month</td>
<td>2 weeks, 1, 2 months, 1 year</td>
<td>6 months</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Wang et al (20), 2002 (China)</td>
<td>Retrospective cohort</td>
<td>7/9</td>
<td>Not reported</td>
<td>117/184</td>
<td>11/15</td>
<td>Not reported</td>
<td>All since 1997</td>
<td>100 IU</td>
<td>1, 2, 7 months</td>
<td>12 months</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Zou et al (22), 2010 (China)</td>
<td>Retrospective cohort/abstract</td>
<td>7/9</td>
<td>Not reported</td>
<td>283/286</td>
<td>12/17</td>
<td>100/-</td>
<td>100/100</td>
<td>200 IU ≤12 h, 2 weeks</td>
<td>Delivery, 1, 6 months</td>
<td>12 months</td>
<td>33</td>
<td>17</td>
</tr>
<tr>
<td>Dwivedi et al (17), 2011 (India)</td>
<td>Retrospective cohort</td>
<td>7/9</td>
<td>Not reported</td>
<td>11/25</td>
<td>2/15</td>
<td>41/-</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>At delivery</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>Lu et al (9), 2012 (Taiwan)</td>
<td>Retrospective cohort/abstract</td>
<td>8/9</td>
<td>Not reported</td>
<td>44/132</td>
<td>1/18</td>
<td>100</td>
<td>74/-</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not stated</td>
<td>Not reported</td>
</tr>
<tr>
<td>Chen et al (16), 2013 (China)</td>
<td>Retrospective cohort</td>
<td>4/9</td>
<td>HIV, HCV, TB, Ig, nuc</td>
<td>98/73</td>
<td>21/14</td>
<td>35/29</td>
<td>100/100</td>
<td>200 IU ≤24 h</td>
<td>s24 h, 1, 6 months</td>
<td>At delivery</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Guo et al (18), 2013 (China)</td>
<td>Case control</td>
<td>7/9</td>
<td>Not reported</td>
<td>584/549</td>
<td>29/72</td>
<td>39/-</td>
<td>69/1</td>
<td>Not reported</td>
<td>Not reported</td>
<td>24 h</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Hu et al (6), 2013 (China)</td>
<td>Retrospective cohort</td>
<td>7/9</td>
<td>HIV, HCV, nuc, threatened abortion</td>
<td>285/261</td>
<td>14/6</td>
<td>25/-</td>
<td>51/100</td>
<td>No dose, s24 h</td>
<td>3 doses total</td>
<td>1–7 years</td>
<td>52</td>
<td>0</td>
</tr>
<tr>
<td>Pan et al (7), 2013 (China)</td>
<td>Retrospective cohort</td>
<td>9/9</td>
<td>HIV, HCV, HDV, nuc/IFN within 6 months</td>
<td>736/673</td>
<td>17/23</td>
<td>55/48</td>
<td>100/100</td>
<td>200 IU ≤6 h</td>
<td>Delivery, 1, 6 months</td>
<td>7–12 months</td>
<td>35</td>
<td>17</td>
</tr>
<tr>
<td>Wen et al (21), 2013 (Taiwan)</td>
<td>Retrospective cohort</td>
<td>8/9</td>
<td>HIV</td>
<td>132/171</td>
<td>3/7</td>
<td>27/-</td>
<td>75/100</td>
<td>100 IU ≤24 h</td>
<td>Within 1 week, 1, 6 months</td>
<td>3 years</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

*All hepatitis B e antigen-positive (HBeAg) women received hepatitis B immune globulin (HBIG) and HBeAg-negative women were given the option to purchase HBIG. HCV Hepatitis C virus; Ig Immunoglobulin; HDV Hepatitis D virus; IFN Interferon; nuc Nucleos(t)ide analogue; TB Tuberculosis*
A subgroup analysis stratified according to 100% HBV vaccination use found only a modest decrease in heterogeneity among studies that had 100% vaccination rates (Q test 9.86; P=0.08; I²=49% [data not shown]). Further stratification within individual studies according to delivery type among women who received appropriate prophylaxis was not possible given the insufficient data. In three studies, data regarding rates of HBV transmission in HBeAg+ women, high risk for transmission, specified by delivery type were available. A separate analysis was performed that suggested a reduction in HBV transmission with Caesarean section but was not statistically significant (OR 0.71 [95% CI 0.47 to 1.08]; low heterogeneity, Q=0.18; P=0.92; I²=0%).

**DISCUSSION**

Using a random-effects pooled meta-analysis, we detected a statistically significant decrease in the overall odds of HBV transmission in women who underwent Caesarean section compared with vaginal delivery. In contrast, a majority of the individual studies had point estimates favoring a reduction in HBV transmission with Caesarean section, but were inconclusive because the 95% CI crossed 1. Our findings are consistent with the findings of meta-analyses before 2012: one was inconclusive and another found a benefit with Caesarean section (23,24). We were able to include six additional studies (3738 newborns) that have been published since 2012, making our meta-analysis the largest and most robust to date.

There was significant heterogeneity among studies, which was largely explained by varying rates of HBIG prophylaxis. In the adjusted meta-regression model, as HBIG use approached 100%, the protective benefit of Caesarean section appeared to decrease, confirming the importance of HBIG in preventing vertical transmission.

Despite demonstrating a benefit in HBV transmission, our findings should be interpreted within the context of the study limitations, particularly given the high heterogeneity and deficits in primary study quality. Although NOS scores were generally high, several of the studies were missing key study details, as depicted in the evidence table (Table 1), and only two studies controlled for confounders such as high viral levels and nucleos(t)ide use. Most studies were conducted in China, with a varying HBeAg+ prevalence and, therefore, may be less generalizable to other countries. Two of the more recent studies (9,22) were only available in abstract form, which significantly limits in-depth analysis. Follow-up periods in several studies spanning decades when HBV prophylaxis was not yet standard of care and many infants may not have received it; this may have elevated the risk for transmission in these studies. HBV transmission also differs in cases of elective compared with urgent Caesarean section for which there is potential for more bleeding and, thus, a greater opportunity for viral transmission. However, this level of detail was not available in most of the studies.

Interpretation of our study findings in the clinical setting is challenging because Caesarean section carries its own complex set of risks. HBIG administration and HBV vaccination should be the first-line measure based on established guidelines (1). All women diagnosed with HBV should be referred to a provider experienced in the management of chronic liver disease (8). Our meta-analysis demonstrated that Caesarean section may offer additional protection against vertical transmission of HBV from the mother to the newborn, but the exact degree of benefit remains uncertain and is heavily influenced by HBIG administration rates. Any protective benefit from Caesarean section most likely occurs in higher-risk mothers, namely those who are HBeAg+ or have persistently elevated DNA levels despite nucleos(t)ide therapy before delivery, and should be studied further. It would be difficult to perform an adequately powered study, which would require 475 women with high viremia who failed nucleos(t)ide therapy, for each delivery method (vaginal versus Caesarean) to have 80% power to detect a decrease in HBV transmission rates from 10% to 5%. Additionally, differences in HBV transmission rates among women undergoing elective versus urgent Caesarean section are still unknown and also require further investigation. Based on fair evidence, we cannot make formal recommendations for or against the use of Caesarean section to prevent transmission of HBV (Grade C). Ultimately, more definitive studies, such as large population-based cohort studies or planned meta-analyses that include 100% HBIG and vaccination use, are needed to confirm our findings before Caesarean section can be adopted in clinical practice as a preventive measure against vertical transmission of HBV.

**ACKNOWLEDGEMENTS:** The authors thank Michael Stoto PhD and Deanna Alexis Carere MA MS CGC CCGC (Harvard School of Public Health) for their meta-analysis guidance.

**DISCLOSURES:** PCA is an employee of Johnson & Johnson Medical, Brazil. The remaining authors have no financial disclosures or conflicts of interest to declare. This study was not funded.

**REFERENCES**
