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Maternal Inactive Hepatitis B Status and Birth-Outcomes: A Systematic Review and Meta-Analysis

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Abstract

Context: Hepatitis is a term used to describe any type of hepatitis inflammation. Screening for the virus antigen during pregnancy is mandatory in some parts of the world and is recommended in others. so that, most women are aware of and understand the disease if they have it when they are pregnant. Thus, the major concerns of these women are both the virus transmission to the fetus and the effects of hepatitis B on pregnancy outcome.

Evidence Acquisition: According to a specific protocol, we searched in the Pub med, Scopus, ISI web of science from 1990 to February 2015 to find the original articles, which investigated the hepatitis B effects in pregnant women with normal singleton pregnancy who were previously diagnosed with inactive CHB or were incidentally found to be HBsAg positive in routine antenatal blood test. We included any cohort, case control and cross sectional studies if they had a healthy control group and reported one or more considered maternal or prinatal outcomes in pregnant women. Meta-analysis was performed with Review manager 5.4 and Stata 11 software. We assessed the effect size that was pooled odds ratio (OR) and 95% confidence intervals (CIs) using the random effects model. We explored statistical heterogeneity using the chi-squared (Chi2), I2 and tau-squared (Tau2) statistical tests.

Results: From a total of 156 identified studies, 56 studies were chosen for a detailed review, and 18 studies which met the inclusion and exclusion criteria were included in the meta analysis. Among the included studies, the outcomes were small for gestational age (SGA) large for gestational age (LGA), intra uterine growth restriction (IUGR), fetal distress, fifth minutes apgar score, first minute Apgar score, low birth weight (LBW) and Fetal Macrosomia.

Conclusions: In this study, hepatitis B had a cause effect on LGA and fetal Macrosomia. Among the other considered adverse pregnancy outcomes; it didn't have any significant effect.

Keywords: Hepatitis B, Neonatal Outcome, Prenatal Outcome

1. Context

Hepatitis is a term used to describe any type of hepatitis inflammation (1). Various factors such as hepatitis viruses, medicines, toxins, alcohol, etc. can lead to hepatitis. Among these, viral hepatitis is one of the main causes of premature death in humans. Babies who are born to infected mothers, intravenous drug users, persons with multiple sexual partners, frequent recipients of blood and blood products, dialysis patients and health personnel are at greater risk. Among viral hepatitis, hepatitis B has become a global problem (2). Despite the progress that has occurred in antiretroviral therapy, the number of people who die due to chronic hepatitis B infection and the number of cancer cases associated with hepatitis B, are increasing (3). It is estimated that about 2 billion people worldwide have serologic evidence of hepatitis B, of which 240 million are chronic carriers and one of which dies due to cirrhosis or hepatocellular carcinoma each year (2). The prevalence of hepatitis B carriers in the world is different, and the difference in the rate of carriers of the disease in different parts of the world is mainly related to age. A patient's age has an inverse relation to the amount of chronic disease so that disease progression from acute hepatitis B infection to chronic infection in the neonatal period is

about 90% (3). In the endemic areas, many adults are infected at birth and the mother-to-child transmission is the dominant method of transmission (4). The virus antigen screening during pregnancy is mandatory in some parts of the world and is recommended in others. so that, most women are aware of and understand the disease if they have it when they are pregnant. Thus, the major concerns of these women are both the virus transmission to the fetus and the effects of hepatitis B on pregnancy outcome (3). Injection of immunoglobulin (HBIG) and the hepatitis B vaccine has been very effective in the prevention of vertical transmission, but there is a little information about the probable hepatitis B effects on newborn outcomes. It was generally accepted that acute or chronic HBV infection did not affect gestation or pregnancy outcome (5, 6). But recent reports, although conflicting, challenge this belief (7). Some studies have suggested a possible effect of hepatitis B on low birth weight, premature rupture of membranes, premature birth, stillbirth, spontaneous abortion and fetal abnormalities (8-15). Since awareness of hepatitis B effects on pregnancy outcomes is important for both patients and health care providers and the study results are controversial, we decided to do this study.

1.2. Objectives

We aimed to reply to this question: Is maternal inactive hepatitis B status associated with adverse pregnancy outcomes such as small for gestational age (SGA), large for gestational age (LGA), fetal distress, apgar score (first and fifth minutes Apgar score if it was under 7, intra -Uterine growth restriction (IUGR), low birth weight (LBW), or fetal Macrosomia?

2. Evidence Acquisition

2.1. Search Strategy

Search strategy was a systematic review which led to a meta-analysis. We searched in the Google scholar, Pub med, Scopus, ISI web of science from 1990 to February 2015. Following the initial screening of titles and abstracts retrieved from the electronic sources, references identified as potentially relevant were examined to find the three key journals. Also, electronic literature searches were supplemented by searching the grey literature (e.g., conference abstracts, thesis, and the result of technical reports) and scanning the reference lists of included studies and relevant systematic reviews. We applied a free keyword or mesh word searching with the following terms: hepatitis B, hepatitis B surface antigen, HbsAg, chronic hepatitis B, CHB, pregnancy outcome, prenatal outcome, prinatal outcome, obstetric outcome, pregnancy adverse effect, neonatal outcome, newborn outcome, small for gestational age (SGA), large for gestational age (LGA), fetal distress, apgar score, intra uterine growth restriction (iugr), low birth weight (LBW), and fetal Macrosomia.

2.2. Criteria for Study Inclusion and Exclusion

We included three types of studies (cohort, case control and cross sectional studies).the inclusion criteria for these studies were: 1, having a healthy control group; 2, reporting one or more considered maternal or birth outcomes.

Patients meeting the following criteria were included: 1, pregnant women who were previously diagnosed with inactive CHB or were incidentally found to be HBsAg positive in routine antenatal blood test; 2, HbsAg+ > 6 months HBeAg; 3, pregnant women with normal singleton pregnancy with no history of disease or medication consumption such as lamivudine, zidovodine etc.

Studies were excluded if a, there was no control group of natural conception; b, obstetric and birth outcomes were not reported; c, the study subjects of primary articles didn't have normal singleton pregnancy, or were addicted; d, super infection with hepatitis A, C, D or E virus was present.

2.3. Data Extraction and Quality Assessment

Two reviewers independently selected the studies and extracted data and outcomes according to inclusion and exclusion criteria (EE AND AK). Title and abstract of the retrieved studies were screened to decide which studies met the inclusion criteria of the meta-analysis. Then, the full texts of the eligible studies were reviewed and the necessary data were extracted and entered into an electronic datasheet. The authors were not blinded to the names of the trials' authors, journals, or results. Any disagreements were resolved through discussion among the authors until consensus was reached. Excluded trials were listed with the reasons for exclusion. If in the primary studies some data were obscured, we sent an email to the author or authors requesting an explanation. Seven items of STROBE checklist were used to assess the risk of bias in the included studies (16). The studies with at most one unclear or inadequate quality component were considered to be studies with low-risk of bias, otherwise as high-risk.

2.4. Methodological Quality Assessment of the Included Studies

For quality assessment, we used the modified version of STROBE (17) which includes seven items of STROBE checklist (setting, participation, variables, bias, limitation and interpretation).There were eight low-risk studies and ten high-risk studies (5, 17-25) among the included studies (Figure 1).

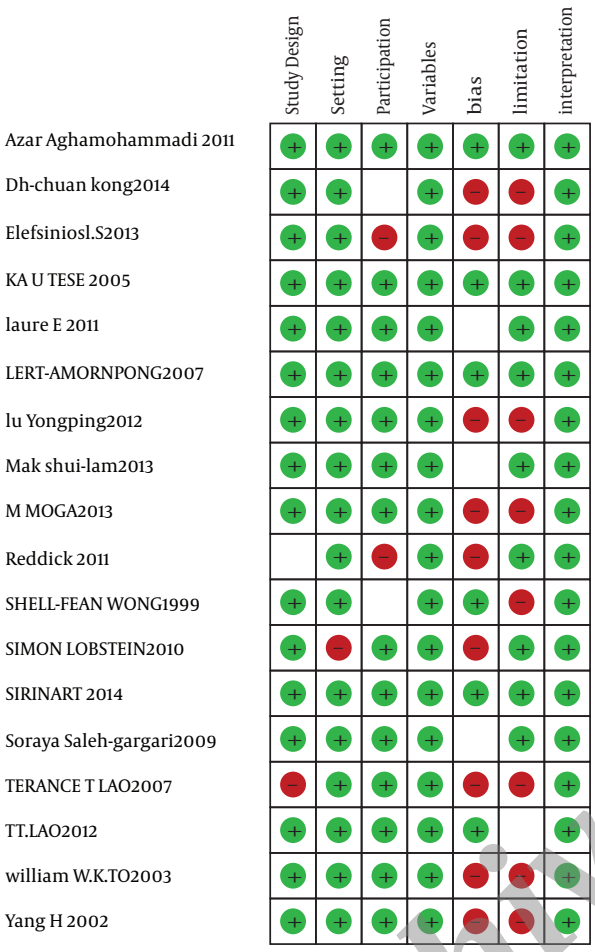

Figure 1. Risk of Bias Summary: Review Authors' Judgments About Each Risk of Bias Item for Each Included Study

2.5. Statistical Analysis

In this study, we used chi-squared (Chi2) test, I2 and tau-squared (Tau2) statistic (26, 27), Begg's and the Egger's tests to statistical heterogeneity, inconsistency across studies, the between-study variance, and publication bias, respectively. The significance level was considered 5% in all areas ($P < 0.05$). Review Manager 5 (28) and Statistical software Stata 11 (Stata Corp, College Station, TX, USA) were employed for data analysis. Data were analyzed and the results were reported using a random effect model (28) with 95% CI.

3. Results

3.1. Search Results

The results of the literature search are summarized in Figure 2.

From a total of 156 identified studies, 56 studies were chosen for a detailed review, and 18 studies which met the inclusion and exclusion criteria were included in the meta analysis. Among the included studies, the characteristics of the included studies are shown in Table 1.

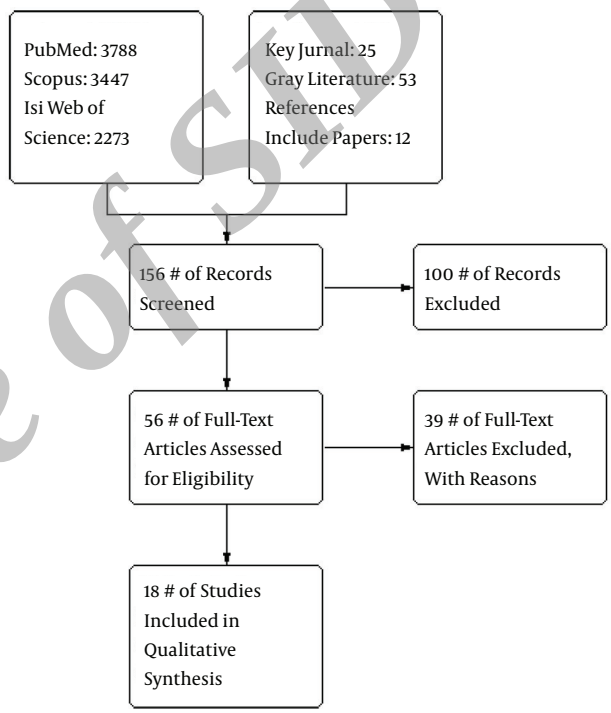

Figure 2. Study Flow Diagram

3.2. Meta-Analysis of Small for Gestational Age (SGA) and Chronic Hepatitis B

Among the six studies in this part, the P value was 0.43 and the corresponding I2 statistic was 0%, suggesting no variability among the studies. The pooled OR was 1.00 (95% CI, 0.93 - 1.07). These findings suggest there is no significant association between inactive CHB infection and SGA. The P values were P = 0.2 and P = 0.1 for the Begg's and the Egger's tests, respectively, indicating no publication bias (Figure 3).

Table 1. The Characteristics of Studies Included in the Meta Analysis

Study	Study Method	Participant No.		Endpoints
		Event	Control	
Aghamohammadi and Nooritajer (2011) (29)	Retrospective -case control	150	200	5th Minutes Apgar Score
Kong et al. (2014) (30)	Case-control	72	956	First and 5th minutes Apgar score, LBW, Macrosomia
Elefsiniotis (2013) (19)	Prospective cohort	70	1926	LBW
Tese (2005) (31)	Case control	253	253	Fetal distress, 5th minutes Apgar score, IUGR
Connell et al. (2011) (26)	Population-based retrospective cohort	1458	1668911	SGA, fetal distress, LBW
Lert-amornpong et al. (2007)(27)	Retrospective case control study	164	162	Fetal distress, 5th minutes Apgar score, IUGR,
LU et al. (2012)(20)	Prospective case control	188	265	LBW, Macrosomia
Moga et al. (2012)(21)	Retrospective case-control	52	111	SGA, LGA,5th minutes Apgar score
Wong et al. (1999) (5)	Case control	824	6281	SGA, fetal distress
MAK (2013) (28)	Retrospective case control	748	8778	First and 5th minutes Apgar score, LBW, Macrosomia
Lobstein et al. (2011) (17)	Retrospective cohort study	39	8154	Fetal distress, IUGR, Macrosomia
Reddick et al. (2011) (22)	Retrospective cohort study	91	1446	IUGR
Sirilert et al. (2014) (32)	Retrospective cohort study	1472	22331	SGA, first and 5th minutes Apgar score, LBW, Macrosomia
Saleh-Gargari et al. (2009) (33)	Retrospective case control	450	450	Fetal distress, first and 5th minutes Apgar score, Macrosomia
Lao et al. (2007) (23)	Retrospective cohort study	6261	55817	SGA,LGA, First and 5th minutes Apgar score, LBW, Macrosomia
Lao et al. (2012) (34)	Retrospective cohort study	8636	77936	SGA, LGA, 5TH Minutes Apgar Score, LBW, Macrosomia
To et al. (2003) (24)	Retrospective case control	1340	12452	5TH minutes Apgar score
Yang et al. (2002)(25)	Case control	81	85	Fetal distress

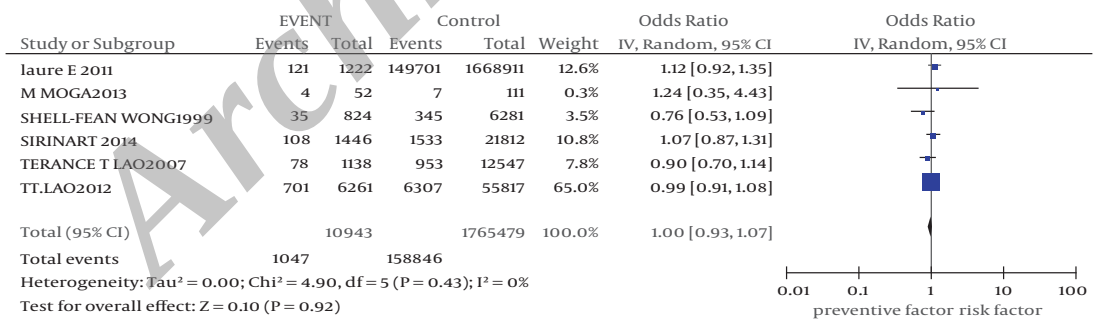

Figure 3. Effect of Chronic Hepatitis B Infection During Pregnancy on the Occurrence of Small for Gestational Age (SGA) using the Random-Effects Model

3.3. Meta-Analysis of Large for Gestational Age (LGA) and Chronic Hepatitis B

In the three studies which compared the incidence of LGA and chronic hepatitis B, the P value was 0.69 and the corresponding I2 statistic was 0%, suggesting no variability among the studies. The total OR was 1.10(95% CI, 1.02 - 1.18). These findings suggest there is probable association between CHB infection and LGA.

The P values were P = 0.6 and P = 0.4 for the Begg's and the Egger's tests, respectively, indicating no publication bias (Figure 4).

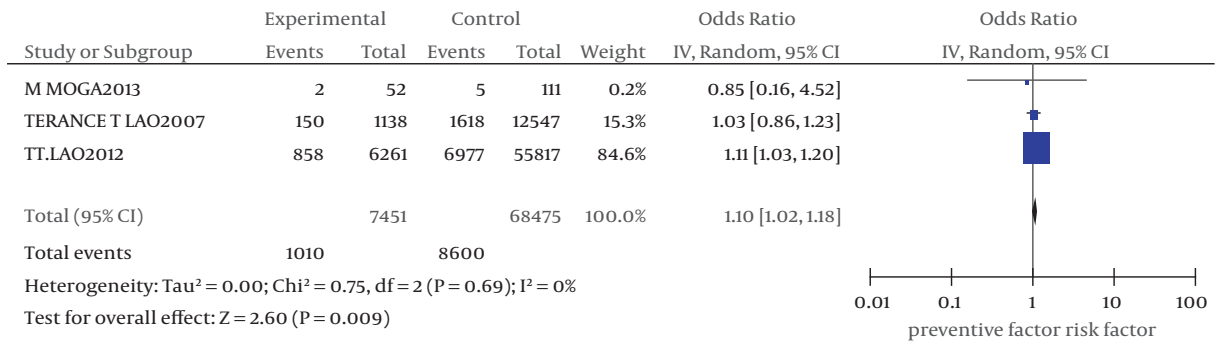

Figure 4. Effect of Chronic Hepatitis B Infection During Pregnancy on the Occurrence of Large for Gestational Age (LGA) Using the Random-Effects Model

3.4. Meta-Analysis of Fetal Distress and Chronic Hepatitis B

In this section, there was low variability according to P value (0.16) and I2 statistic (35%), and the effect size measure (OR) was 1.44 (95% CI, 1.00 - 2.08). As a statistical view, this indicates there is no significant association between inactive CHB infection and SGA. Taking a closer look at the confidence interval, we can conclude inactive chronic hepatitis can increase the chance of fetal distress. The P values were P = 0.3 and P = 0.2 for the Begg's and the Egger's tests, respectively, indicating no publication bias (Figure 5).

3.5. Meta-Analysis of the First Minute Apgar Score if it was Under 7, and Chronic Hepatitis B

There were five studies which compared the first minute Apgar score under 7. The P value was 0.78 and the corresponding I2 statistic was 0%, suggesting no variability among the studies.

The total OR was 0.90 (95% CI, 0.78 - 1.04). According to these statistical tests, there was no significant association between CHB infection and first minute Apgar score under 7. The P values were P = 0.1 and P = 0.2 for the Begg's and the Egger's tests, respectively, indicating no publication bias (Figure 6).

3.6. Meta-analysis of the Fifth Minutes Apgar Score (If It Was Under 7) and Chronic Hepatitis B

The eleven primary studies comparing this outcome indicated low variability. The (P value was 0.13 and the corresponding I2 was 35%). The pooled OR was 1.07(95% CI, 0.82 - 1.19). These findings suggest there is no significant association between CHB infection and fifth minutes Apgar score under 7. The P values were P = 0.4 and P = 0.2 for the Begg's and the Egger's tests, respectively, indicating no publication bias (Figure 7).

3.7. Meta-analysis of Intra-Uterine Growth Restriction (IUGR) and Chronic Hepatitis B

The statistics showed that the four studies in this group were homogenous (The P value was 0.59 and the corresponding I2 statistic was 0%). The Meta-analysis showed that the pooled OR was 1.24 (95% CI, 0.81 - 1.88). These findings suggest there is no significant association between CHB infection and IUGR. The P values were P = 0.1 and P = 0.2 for the Begg's and the Egger's tests, respectively, indicating no publication bias (Figure 8).

3.8. Meta-Analysis of Low Birth Weight (LBW) and Chronic Hepatitis B

Among eight of the eighteen studies which compared the LBW between the chronic hepatitis B and healthy pregnant women groups, the amount of I2 (89%) and (P < 0.0001) showed severe heterogeneity. The P values were P = 0.3 and P = 0.1 for the Begg's and the Egger's tests, respectively, indicating no publication bias. The total OR indicatedno significant association between CHB infection and IUGR (Figure 9) (OR = 0.93 CI95%, 0.68 - 1.25)

We conducted two subgroup analyses based on study design and quality but I2 did not decrease in any study groups (Figures 9, 10).

3.9. Meta-Analysis of Macrosomia and Chronic Hepatitis B

According to the statistical results, the occurrence of macrosomia in the hepatitis B infected women was little more than non-infected women (OR = 1.14 CI95%: 1.02 - 1.26), there was moderate variability among the eight studies in this part (I2 = 57%, P = 0.02)

We conducted two subgroup analyses based on the quality and design of the included studies in this section. Analysis could decrease the amount of I2 only in cohort and low quality study group in each part. The P values were

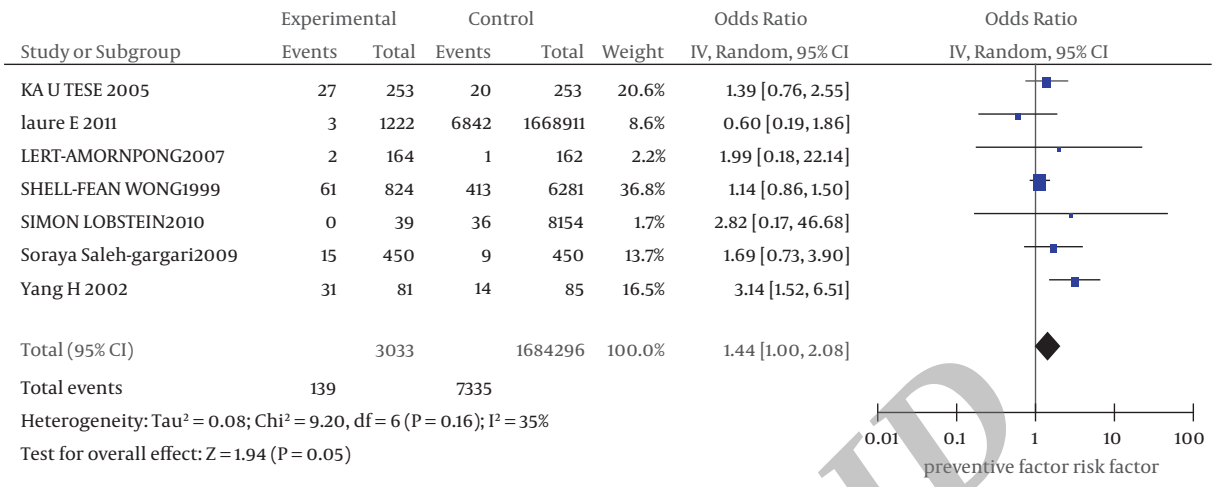

Figure 5. Effect of Chronic Hepatitis B Infection During Pregnancy on the Occurrence of Fetal Distress Using the Random-Effects Model

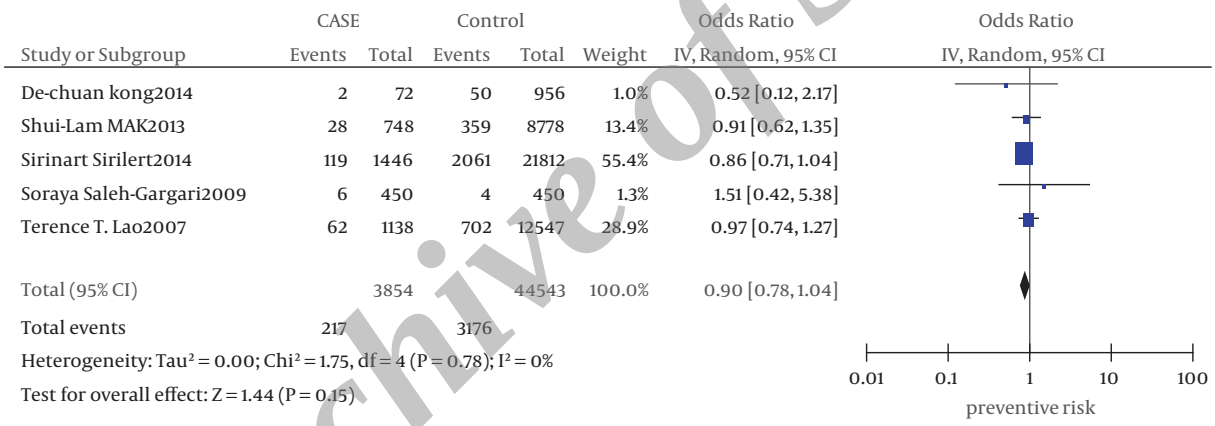

Figure 6. Effect of Chronic Hepatitis B Infection During Pregnancy on the Occurrence of the First Minute Apgar Score Under 7, Using the Random-Effects Model

P = 0.2 and P = 0.1 for the Begg's and the Egger's tests, respectively, indicating no publication bias (Figures 11, 12).

4. Conclusions

Hepatitis B is one of the most important issues in the field of reproductive health. Since in many countries screening for hepatitis B happens during pregnancy, the majority of mothers are concerned about the effect of hepatitis B on their baby (28).

As the results showed, with the exceptions of LGA and macrosomia, hepatitis B did not increase the risk of the other adverse outcomes. Lao et al. showed in their studies that, the probable association between hepatitis B and infant size can be because of gestational diabetes mellitus (23, 24). Primary articles also found that hepatitis B interacted in different manners with different maternal factors with the ultimate effect of increasing fetal growth even in the low risk pregnancies (34).

The studies which indicated a significant effect of hepatitis B on pregnancy outcome, agreed that the systemic inflammation caused by the hepatitis B is responsible for unwanted pregnancy complications (6, 20, 25, 26). But some of the other studies denied these effects and believed that there is a low risk of the transmission of hepatitis B through the placenta, indicating these pregnancies are the same as non-infected pregnancies (17, 23, 28, 31).

One important point in these studies involves the pos-

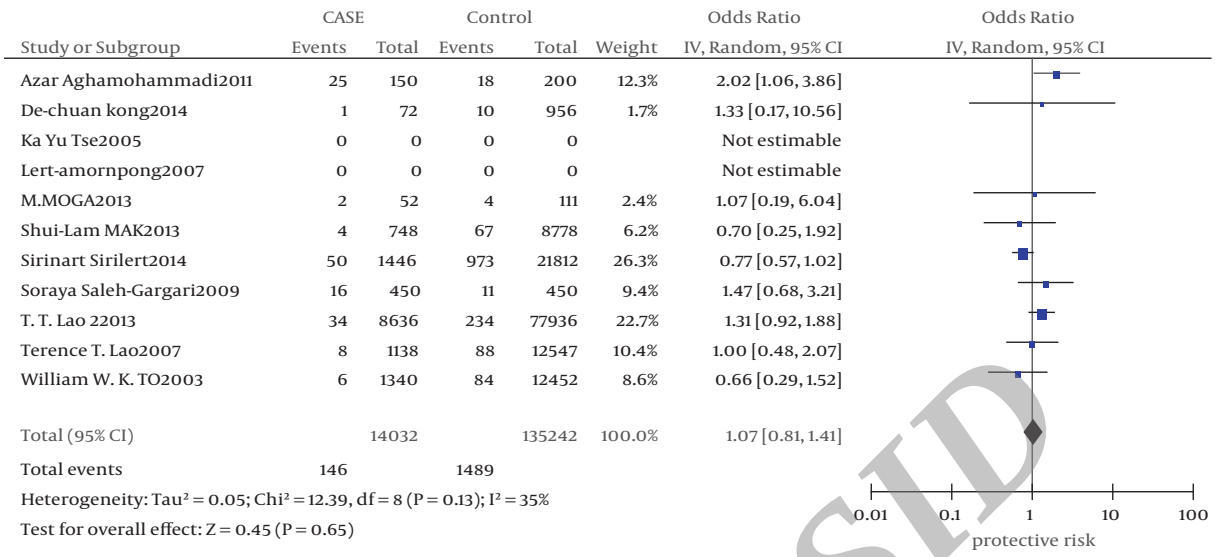

Figure 7. Effect of Chronic Hepatitis B Infection During Pregnancy on the Occurrence of the Fifth Minutes Apgar Score Under 7, Using the Random-Effects Model

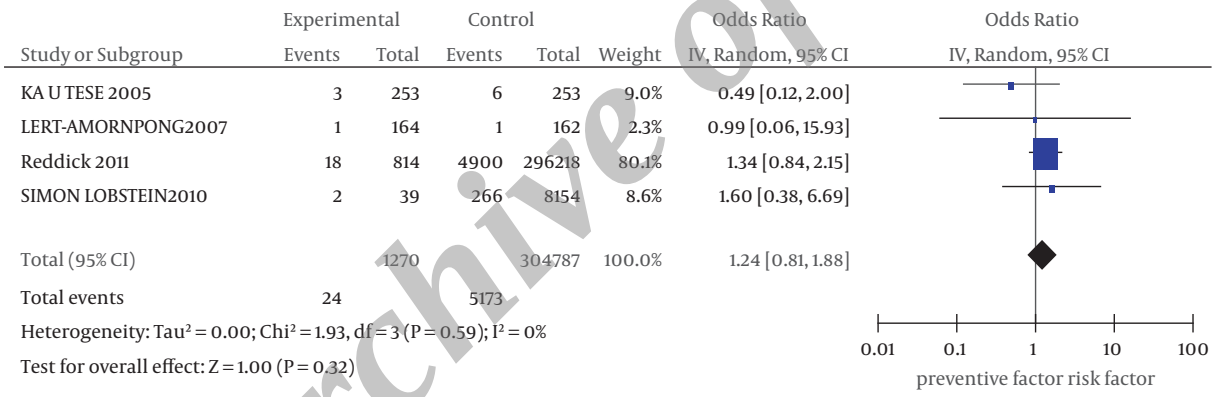

Figure 8. Effect of Chronic Hepatitis B Infection During Pregnancy on the Occurrence of Intra -Uterine Growth Restriction (IUGR), Using the Random-Effects Model

sible effect of the study area on the study results (5, 22). Small studies in non-endemic areas might not be able to address the adverse outcomes. Unfortunately, we did not have enough studies for investigating this hypothesis. In-addition to this point, one of the non-effect studies implies that hepatitis B don't have any effect on placental function so that it didn't increase the rate of pregnancy adverse effects.

Looking at the results regarding SGA, IUGR, and LBW indications that hepatitis B is not associated with additional risks of the considered outcomes during pregnancy. In regards Macrosomia and LGA, results showed an increased risk of these adverse effects in the inactive CHB infection group. This conclusion should be expressed with caution because of the heterogeneity.

In the group of SGA, LGA and IUGR, I2 was 0%, which suggested no variability among the studies. But in regards to LBW and Macrosomia, there was evidence of heterogeneity (small P value of Chi2 test and large I2 statistic). The heterogeneity varied from moderate (I2 = 61% and P = 0.02 for Chi2 test) to severe (I2 = 89% and P < 0.0001 for Chi2 test).It is a fact that the Chi2, this test has low power when the sample size (the number of studies in each group) is low. On the other hand, in the situation of a low sample size, the test has high power in detecting a small amount of heterogeneity which may be clinically unimportant as was the case

in our review. Therefore, we can attribute part of the observed heterogeneity to the number of studies included in the meta-analysis. Another reason which can be proposed to explain the observed heterogeneity is the presence of remarkable difference between the studies' results. For evaluating the source of variability we conducted two sub group analyses based on the study design and quality. This analysis in the section of LBW and hepatitis B did not show decrease in the amount of I2. Moreover, the Tau2 statistic, which was used to investigate the variances between studies, was small and equal to 0.12. what may explain this paradox is that Tau2 would decrease when the between-studies variance is low and hence ,the within-studies variance is high (35, 36).

It is correct that subgroup analyses could not decrease the amount of I2 in the section of Macrosomia, but greater precision in its Forest plot showed that after quality sub grouping, the studies have have moved toward homogenization. Even if the Saleh-Gargary et al. and Simon-Lobstein et al. studies - which have a wide confidence interval –were not entered in the analysis the amount of I2 decreased in both analysis groups.(I2 = 6% in high quality group AND I2 = 27% in low quality group).

Because Apgar score is one of the primary newborn health indicators, we were curious to see the effects of hepatitis B on it. Unfortunately, the articles reported this outcome in different ways. We sent a lot of messages to the studies' author but it didn't have any benefit for us. Therefore, in this area we evaluated the articles which reported similar results.

The study results in these two parts suggest there is no effect of hepatitis B on the first and fifth minutes Apgar score. In the reports of papers which agreed there is significant effect of the disease on Apgar score ,the higher incidence of preterm labor was considered as justification of this relation (19, 25). We did not encounter the existence of any heterogeneity between the studies involving the first minute Apgar score. In the other section there was low heterogeneity (I2 = 35%) .When we look at the forest plot, we find that only one study (Sirinert's et al. study) announced different results. If this study is not included in tour, analysis the amount of I2 changes to 0%.

Our final result relates to fetal distress. The statistical analysis in this part showed that hepatitis B cannot be a risk factor for fetal distress. There was a low heterogeneity among the included studies (I2 = 35%), but from a clinical view it can increase the risk. Primary studies in this part have a wide confidence interval indicating variety of situations will cause fetal distress, calling for the need of more accurate studies to accurately verify this relation. In regards to justification the Yang et al. study declared hepatitis B infection in pregnant women can accompany with preeclampsia, severe anemia or placental chorionic disease, which are associated with Fetal Distress (25).

This study was one of the few studies that attempted to evaluate the adverse effects of hepatitis B on Birth outcomes, but it had some limitations. The first limitation was importing low-quality studies. The reason for this limitation was the small number of studies which had been conducted in this area. The other limitation was related to the nature of hepatitis B. Hepatitis B is endemic in some countries, such as China, and there have been many studies conducted in these countries but there are no English abstracts for them, necessitating searches in their native languages.

In this study, hepatitis B had a cause effect on LGA and macrosomia. Among the other considered adverse pregnancy outcomes, it did not have any significant effect. But, these conclusions should be assessed with further well designed studies.

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Footnotes

Conflict of Interest: The authors declare no conflict of interest in this study.

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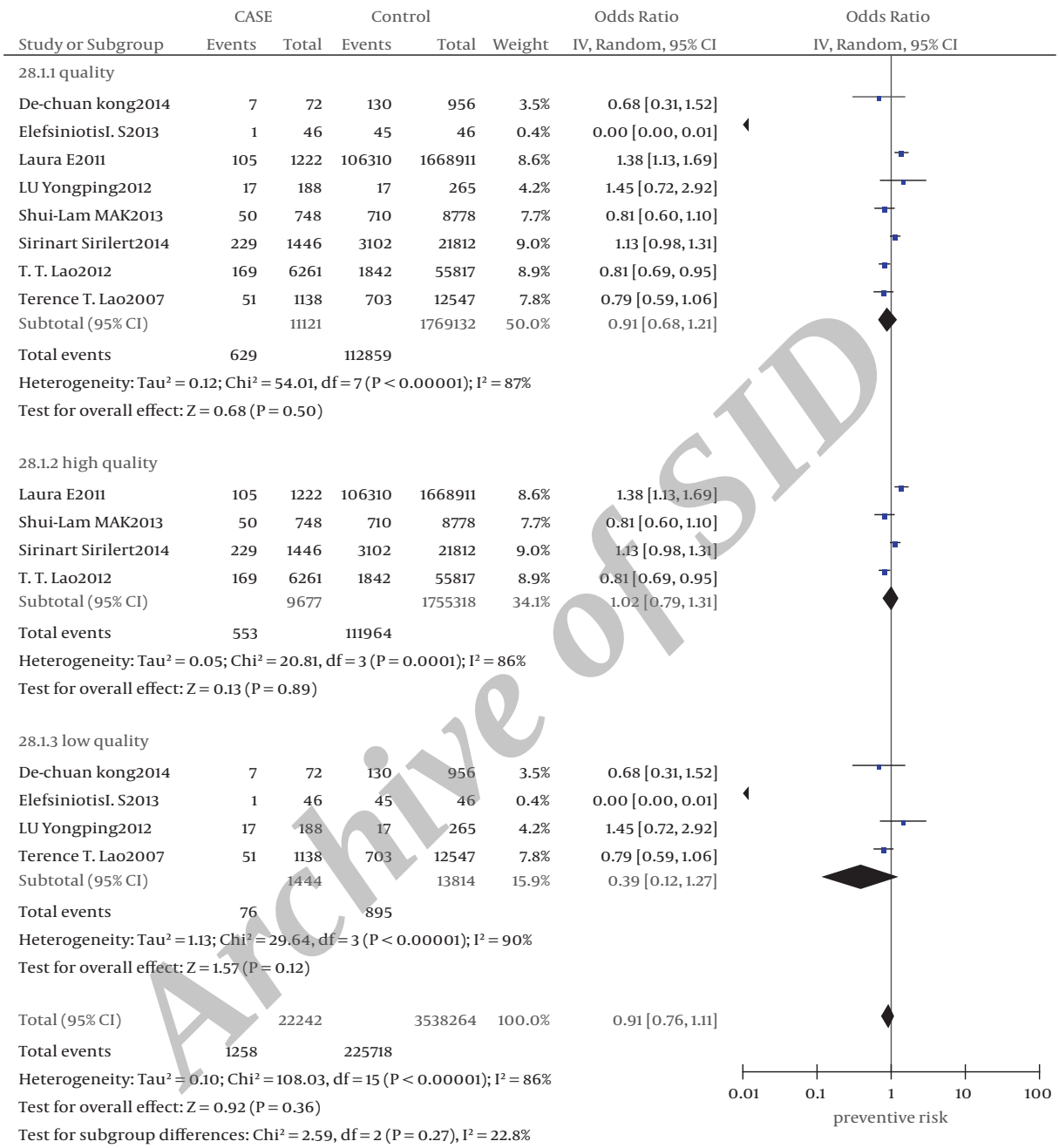

Figure 9. Effect of Chronic Hepatitis B Infection During Pregnancy on the Occurrence of Low Birth Weight (LBW), Using a Random-Effects Model. (Sub-Group Analysis Based on Study Quality)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio IV, Random, 95% CI
6.1.1 study design						
Dh-chuan kong2014	7	72	130	956	3.5%	0.68 [0.31, 1.52]
Elefsiniosl.S2013	1	46	45	46	0.4%	0.00 [0.00, 0.01]
laure E 2011	105	1222	106310	1668911	8.6%	1.38 [1.13, 1.69]
lu Yongping2012	17	188	17	265	4.2%	1.45 [0.72, 2.92]
Mak shui-lam2013	50	748	710	8778	7.7%	0.81 [0.60, 1.10]
SIRINART 2014	229	1446	3102	21812	9.0%	1.13 [0.98, 1.31]
TERANCE T LAO2007	51	1138	703	12547	7.8%	0.79 [0.59, 1.06]
TT.LAO2012	169	6261	1842	55817	8.9%	0.81 [0.69, 0.95]
Subtotal (95% CI)		11121		1769132	50.0%	0.91 [0.68, 1.21]
Total events	629		112859			
Heterogeneity: Tau² = 0.12; Chi² = 54.01, df = 7 (P < 0.00001); I² = 87%						
Test for overall effect: Z = 0.68 (P = 0.50)						
6.1.2 cohort						
laure E 2011	105	1222	106310	1668911	8.6%	1.38 [1.13, 1.69]
SIRINART 2014	229	1446	3102	21812	9.0%	1.13 [0.98, 1.31]
TERANCE T LAO2007	51	1138	703	12547	7.8%	0.79 [0.59, 1.06]
TT.LAO2012	169	6261	1842	55817	8.9%	0.81 [0.69, 0.95]
Subtotal (95% CI)		10067		1759087	34.2%	1.01 [0.78, 1.30]
Total events	554		111957			
Heterogeneity: Tau² = 0.06; Chi² = 21.57, df = 3 (P < 0.0001); I² = 86%						
Test for overall effect: Z = 0.08 (P = 0.94)						
6.1.3 case control						
Dh-chuan kong2014	7	72	130	956	3.5%	0.68 [0.31, 1.52]
Elefsiniosl.S2013	1	46	45	46	0.4%	0.00 [0.00, 0.01]
lu Yongping2012	17	188	17	265	4.2%	1.45 [0.72, 2.92]
Mak shui-lam2013	50	748	710	8778	7.7%	0.81 [0.60, 1.10]
Subtotal (95% CI)		1054		10045	15.8%	0.39 [0.12, 1.28]
Total events	75		902			
Heterogeneity: Tau² = 1.14; Chi² = 29.64, df = 3 (P < 0.00001); I² = 90%						
Test for overall effect: Z = 1.55 (P = 0.12)						
Total (95% CI)		22242		3538264	100.0%	0.91 [0.76, 1.11]
Total events	1258		225718			
Heterogeneity: Tau² = 0.10; Chi² = 108.03, df = 15 (P < 0.00001); I² = 86%						
Test for overall effect: Z = 0.92 (P = 0.36)						
Test for subgroup differences: Chi² = 2.48, df = 2 (P = 0.29), I² = 19.3%						

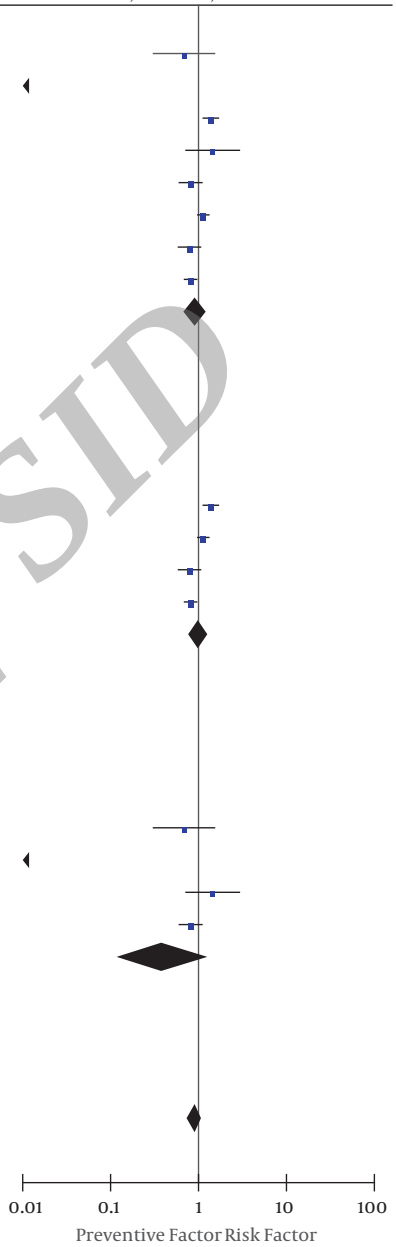

Figure 10. Effect of Chronic Hepatitis B Infection During Pregnancy on the Occurrence of Low Birth Weight (LBW), Using a Random-Effects Model. (Sub-Group Analysis Based on Study Design)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
7.1.1 study design						
Dh-chuan kong2014	5	72	36	956	0.4%	1.91 [0.72, 5.02]
lu Yongping2012	8	188	12	265	0.7%	0.94 [0.38, 2.34]
Mak shui-lam2013	24	748	305	8778	3.6%	0.92 [0.60, 1.40]
SIMON LOBSTEIN2010	1	39	50	8154	0.0%	4.27 [0.57, 31.67]
SIRINART 2014	53	1446	787	21812	7.4%	1.02 [0.77, 1.35]
Soraya Saleh-gargari2009	30	450	10	450	0.7%	3.14 [1.52, 6.51]
TERANCE T LAO2007	34	1138	464	12547	5.9%	0.80 [0.56, 1.14]
TT.LAO2012	275	6261	2065	55817	31.2%	1.20 [1.05, 1.36]
Subtotal (95% CI)		10342		108779	50.0%	1.14 [1.02, 1.26]
Total events	430		3729			
Heterogeneity: Chi² = 16.33, df = 7 (P = 0.02); I² = 57%						
Test for overall effect: Z = 2.39 (P = 0.02)						
7.1.2 cohort						
SIMON LOBSTEIN2010	1	39	50	8154	0.0%	4.27 [0.57, 31.67]
SIRINART 2014	53	1446	787	21812	7.4%	1.02 [0.77, 1.35]
TERANCE T LAO2007	34	1138	464	12547	5.9%	0.80 [0.56, 1.14]
TT.LAO2012	275	6261	2065	55817	31.2%	1.20 [1.05, 1.36]
Subtotal (95% CI)		8884		98330	44.5%	1.12 [1.00, 1.25]
Total events	363		3366			
Heterogeneity: Chi² = 6.59, df = 3 (P = 0.09); I² = 55%						
Test for overall effect: Z = 1.95 (P = 0.05)						
7.1.3 case control						
Dh-chuan kong2014	5	72	36	956	0.4%	1.91 [0.72, 5.02]
lu Yongping2012	8	188	12	265	0.7%	0.94 [0.38, 2.34]
Mak shui-lam2013	24	748	305	8778	3.6%	0.92 [0.60, 1.40]
Soraya Saleh-gargari2009	30	450	10	450	0.7%	3.14 [1.52, 6.51]
Subtotal (95% CI)		1458		10449	5.5%	1.29 [0.95, 1.74]
Total events	67		363			
Heterogeneity: Chi² = 9.28, df = 3 (P = 0.03); I² = 68%						
Test for overall effect: Z = 1.63 (P = 0.10)						
Total (95% CI)		20684		217558	100.0%	1.14 [1.05, 1.22]
Total events	860		7458			
Heterogeneity: Chi² = 32.65, df = 15 (P = 0.005); I² = 54%						
Test for overall effect: Z = 3.38 (P = 0.0007)						
Test for subgroup differences: Chi² = 0.74, df = 2 (P = 0.69), I² = 0%						

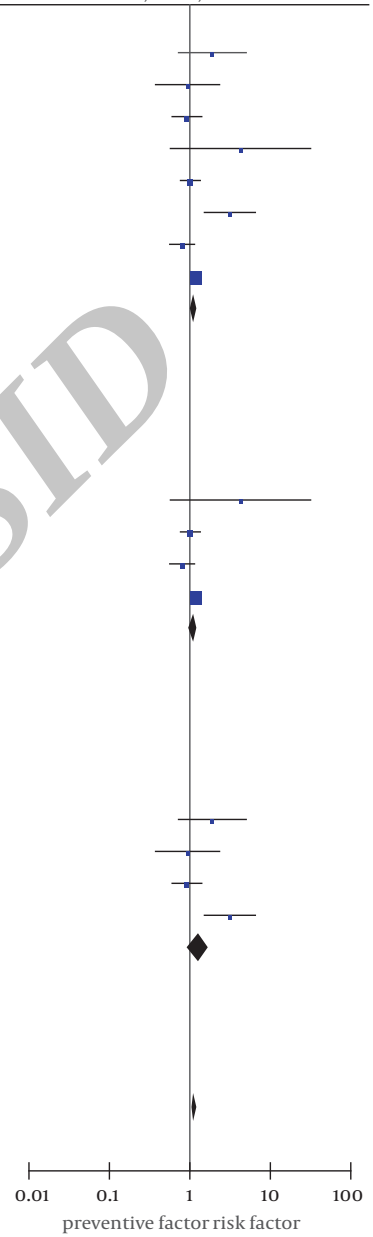

Figure 11. Effect of Chronic Hepatitis B Infection During Pregnancy on the Occurrence of Macrosomia, Using the Random-Effects Model. (Sub -Group Analysis Based on Study Design)

Study or Subgroup	CASE Events	Total	Control Events	Total	Weight	Odds Ratio IV, Random, 95% CI
30.1.1 New Subgroup						
De-chuan kong2014	5	72	36	956	2.1%	1.91 [0.72, 5.02]
LU Yongping2012	8	188	12	265	2.3%	0.94 [0.38, 2.34]
Shui-Lam MAK2013	24	748	305	8778	7.2%	0.92 [0.60, 1.40]
Simon Lobstein2010	1	39	50	8154	0.5%	4.27 [0.57, 31.67]
Sirinart Sirilert2014	53	1446	787	21812	10.6%	1.02 [0.77, 1.35]
Soraya Saleh-Gargari2009	30	450	10	450	3.3%	3.14 [1.52, 6.51]
T. T. Lao2012	275	6261	2065	55817	15.3%	1.20 [1.05, 1.36]
Terence T. Lao2007	34	1138	464	12547	8.7%	0.80 [0.56, 1.14]
Subtotal (95% CI)		10342		108779	50.0%	1.15 [0.90, 1.46]
Total events	430		3729			
Heterogeneity: Tau² = 0.05; Chi² = 16.32, df = 7 (P = 0.02); I² = 57%						
Test for overall effect: Z = 1.13 (P = 0.26)						
30.1.2 high quality						
Shui-Lam MAK2013	24	748	305	8778	7.2%	0.92 [0.60, 1.40]
Sirinart Sirilert2014	53	1446	787	21812	10.6%	1.02 [0.77, 1.35]
Soraya Saleh-Gargari2009	30	450	10	450	3.3%	3.14 [1.52, 6.51]
T. T. Lao2012	275	6261	2065	55817	15.3%	1.20 [1.05, 1.36]
Subtotal (95% CI)		8905		86857	36.4%	1.20 [0.90, 1.59]
Total events	382		3167			
Heterogeneity: Tau² = 0.05; Chi² = 9.37, df = 3 (P = 0.02); I² = 68%						
Test for overall effect: Z = 1.26 (P = 0.21)						
30.1.3 low quality						
De-chuan kong2014	5	72	36	956	2.1%	1.91 [0.72, 5.02]
LU Yongping2012	8	188	12	265	2.3%	0.94 [0.38, 2.34]
Simon Lobstein2010	1	39	50	8154	0.5%	4.27 [0.57, 31.67]
Terence T. Lao2007	34	1138	464	12547	8.7%	0.80 [0.56, 1.14]
Subtotal (95% CI)		1437		21922	13.6%	1.12 [0.65, 1.93]
Total events	48		562			
Heterogeneity: Tau² = 0.13; Chi² = 5.01, df = 3 (P = 0.17); I² = 40%						
Test for overall effect: Z = 0.39 (P = 0.70)						
Total (95% CI)		20684		217558	100.0%	1.13 [0.98, 1.31]
Total events	860		7458			
Heterogeneity: Tau² = 0.03; Chi² = 32.64, df = 15 (P = 0.005); I² = 54%						
Test for overall effect: Z = 1.63 (P = 0.10)						
Test for subgroup differences: Chi² = 0.08, df = 2 (P = 0.96), I² = 0%						

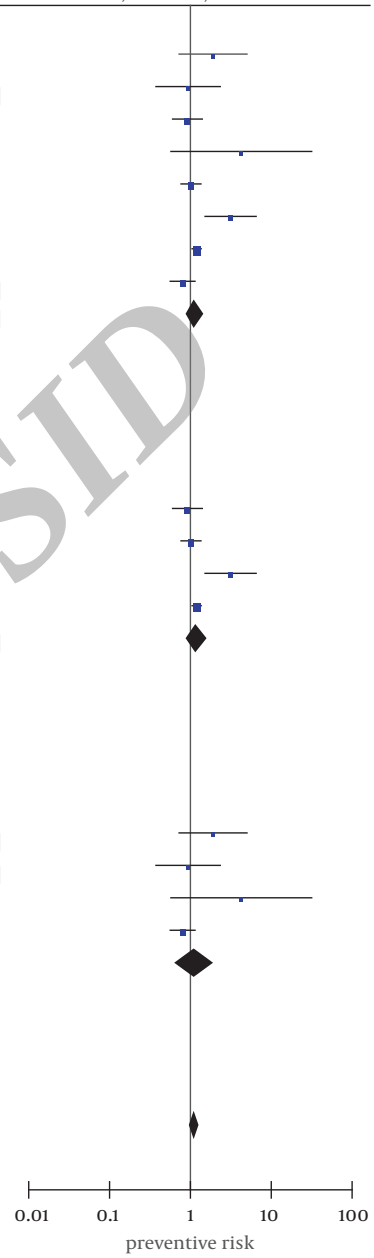

Figure 12. Effect of Chronic Hepatitis B Infection During Pregnancy on the Occurrence of Macrosomia, Using a Random Effects Model. (Sub -Group Analyses Based on Study Quality)