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Case-fatality risk of pregnant women with acute viral hepatitis type E: a systematic review and meta-analysis

H. JIN[1,2]*, Y. ZHAO[2], X. ZHANG[3], B. WANG[3] AND P. LIU[2]

[1] *Department of Epidemiology and Health Statistics, School of Public Health, Southeast University, Nanjing, China*
[2] *Key Laboratory of Environmental Medicine Engineering, Ministry of Education, School of Public Health, Southeast University, Nanjing, China*
[3] *Jiangsu Provincial Center for Disease Control and Prevention, China*

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SUMMARY

It is of great concern that pregnant women with acute viral hepatitis (AVH) type E have serious consequences. This study aimed to estimate the case-fatality risk (CFR) and potential risk factors of pregnant women with AVH type E. We searched the PubMed, EMBASE, and Web of Science databases for studies containing data on CFR in pregnancy with AVH type E. A pooled estimate of CFR was calculated using a random-effects model. Potential sources of heterogeneity were explored using subgroup analysis, sensitivity analysis, and meta-regression. We identified 47 eligible studies with a total African and Asian population of 3968 individuals. The pooled CFRs of maternal and fetal outcomes were 20·8% [95% confidence interval (CI) 16·6–25·3] and 34·2% (95% CI 26·0–43·0), respectively. Compared with these, the pooled CFR was highest (61·2%) in women with fulminant hepatic failure (FHF). Community-based surveys had lower pooled CFR (12·2%, 95% CI 9·2–15·6) and heterogeneity (25·8%, 95% CI 20·1–32·0) than hospital-based surveys. Univariate analysis showed that hospital-based surveying ($P = 0·007$), and patients in the third trimester of pregnancy or with FHF ($P < 0·05$), were significantly associated with CFR. Intrauterine fetal mortality (27·0%) was statistically higher than neonatal mortality (3·9%). Control measures for HEV infection would reduce feto-maternal mortality in Asia and Africa.

Key words: Acute viral hepatitis E, case-fatality risk, meta-analysis, pregnancy.

INTRODUCTION

Hepatitis E virus (HEV) is established as a major cause of acute viral hepatitis (AVH) worldwide [1]. Most deaths caused by AVH type E occur in resource-poor countries in Asia, Africa, and Latin America, where exposure to water contaminated with faeces results in outbreaks and sporadic cases of hepatitis E [2]. Usually, acute HEV infection in humans is self-limiting, shows no evidence of chronic HEV infection, and has a case-fatality rate of <4% [3]. However, the case-fatality risk (CFR) is much higher in pregnant women (15–25%) [3], particularly during the third trimester [2, 3] in areas where HEV genotypes 1 and 2 are endemic.

Emerging evidence from epidemiological and clinical studies suggests that incidence, morbidity and mortality of hepatitis E are high in pregnancy [1–4]. Furthermore, vertical transmission of HEV may occur frequently in mothers with hepatitis E, and contribute to serious perinatal health outcomes. A recent

* Author for correspondence: Mr H. Jin, Department of Epidemiology and Health Statistics, School of Public Health, Southeast University, Nanjing, 210009, China.
(Email: jinhui_hld@163.com)

study estimated that in 2005, in 9/21 Global Burden of Disease regions, there were 3000 stillbirths as a consequence of HEV infection [1]. The global burden of disease associated with hepatitis E may be underestimated, as another recent study has suggested that there may be ~1000 maternal deaths per annum in Bangladesh alone [4]. However, the pathophysiological basis of increased mortality in pregnancy and of the fetus is not well understood.

The CFR is the probability that an infection results in death. For an emerging infectious disease, the CFR is a vital metric to assess clinical severity and influence the public health measures put in place to control an epidemic [5, 6]. Among pregnant women infected with HEV, the severity can be quantified by assessing the risk of disease progression. However, the WHO suggested that the absence of such information presented an obstacle to understanding the consequences of HEV infections on maternal, fetal, and neonatal outcomes (http://www.who.int/wer/2015/wer9018.pdf). An understanding of disease complications can help to formulate effective strategies for disease prevention, control and patient management leading to better feto-maternal outcome. Therefore, this study aimed to estimate the CFR of pregnant women with AVH type E and to determine its effect on perinatal morbidity and mortality using meta-analysis.

METHODS

This systematic review followed the PRISMA [Preferred Reporting Items for Systematic Reviews and Meta-Analyses] guidelines (Supplementary Table S1).

Search strategy and selection criteria

A literature search was performed using the PubMed, EMBASE and Web of Science databases without language restrictions on 28 December 2014. Search terms included '(hepatitis E* OR HEV) AND (pregnan* OR women OR mother OR infant OR child OR fetal OR perinatal)', which were entered into the abstract/title/keywords sections (Supplementary Table S2). The bibliographies of original studies, reviews, and relevant conferences were manually searched.

The inclusion criteria were: (1) surveillance for HEV with information on the period and geographical region of investigation, including retrospective and prospective studies; and (2) the number of reported cases and deaths of laboratory-confirmed AVH associated with HEV on the basis of population or hospital studies. Maternal deaths were defined as those that occurred during pregnancy or within 42 days following a birth, stillbirth, or miscarriage. A neonatal death was defined as a death occurring within 28 days of birth.

Acute hepatitis E virus infection was diagnosed by the detection of HEV-RNA or IgM anti-HEV antibodies when the patient presented with a combination of (*a*) recent-onset jaundice in the absence of a history of jaundice or chronic liver disease; (*b*) no other cause to account for jaundice, including drug-induced hepatitis, severe infections, and cholestatic jaundice during pregnancy; and (*c*) elevation of serum alanine transferase level 2·5 times the upper limit of the normal range. The disease was considered as fulminant hepatic failure (FHF) when, after a typical acute onset period, a patient with no history of chronic liver disease became deeply jaundiced and developed hepatic encephalopathy within 8 weeks. Encephalopathy was graded using the West Haven criteria. Fatality was defined as the death of the mother during pregnancy or within 42 days postpartum due to AVH or FHF.

For studies that had been repeated, only the most recent and detailed was included in the analysis.

Data extraction and quality assessment

Two researchers (H.J. and Y.Z.) independently evaluated the studies and extracted the data. The extracted data included the period and geographical region of investigation. The number of cases of AVH, deaths by AVH caused by HEV infection, causes of death, proportion of laboratory-confirmed AVH cases associated with HEV (reported cases were used), fetal outcomes, etc. were all included in the analysis.

The quality of each study was independently assessed by two investigators (H.J. and Y.Z.) according to the STROBE statement [7]. A STROBE-based checklist including six criteria was used to assess the risk of bias in each study [8]. A consensus was determined with the help of a third author (B.W.), if necessary.

Statistical analysis

A random-effects model was used for summary statistics because of the high level of heterogeneity ($I^2 >$ 75%) [9]. The CFR (%) of the studies was calculated on the basis of a double arcsine transformation before pooling if CFR data was not normal. Subsequently, a

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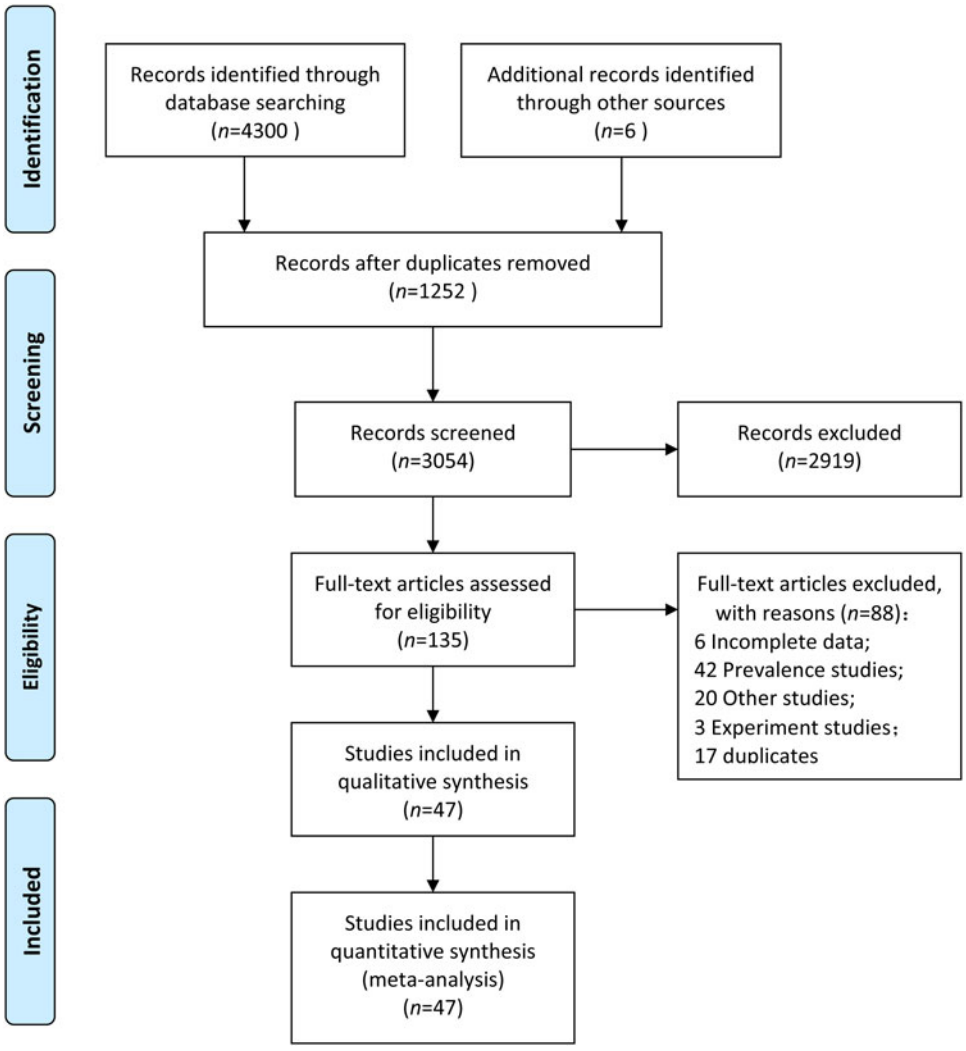

Fig. 1. Selection of 47 articles for a study of the case-fatality risk of pregnant women with acute viral hepatitis E, 1986–2014.

forest plot was used to indicate the point estimation of CFR and the 95% confidence interval (CI). We estimated the heterogeneity between the studies using Cochran's Q and the I^2 statistic.

Subgroup analysis was performed according to the period and geographical region of investigation, source, severity of disease, and risk of bias. Sensitivity analysis was performed to evaluate the impact of the included studies. Univariate analysis was conducted considering several factors, including the period and geographical region of investigation, severity of disease, and source. Potential sources of heterogeneity were further investigated using meta-regression analysis, in which the included variables were statistically significant ($P < 0{\cdot}05$) in univariate analysis.

A normality test and meta-analysis were conducted using R i386 3·1·0 software [10], and other analyses were performed using Stata software v. 13.0 (Stata Corporation, USA).

RESULTS

A total of 4306 titles and abstracts were screened, and 135 full articles were retrieved. Forty-seven eligible studies ($n = 3968$ patients) were included in the analysis (Fig. 1). All included studies came from epidemic areas, most of which were potentially associated with faecally contaminated drinking water. These studies reported the CFR of pregnant women with AVH in Asia (37 studies) and Africa (10 studies). The included studies mainly reported findings from hospital-based

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Table 1. *Study characteristics for 47 articles of the case-fatality risk of pregnant women with acute viral hepatitis type E*

Study characteristic	No. of studies		
	Community-based	Hospital-based	Total
Total no. of studies	16	31	47
Total no. of participants	1772	2196	3968
Geographical region			
Africa	6	4	10
Asia	10	27	37
Type of test			
ELISA	11	20	31
ELISA, PCR	3	4	7
unknown	2	7	9
Risk of bias			
Moderate	1	2	3
High	15	16	31
Very high	0	13	13

populations (66·0%) (Table 1, Supplementary Tables S3–S4).

Of the 47 included studies, three had a moderate risk of bias, 31 had a high risk of bias, and 13 had a very high risk of bias according to the previously described criteria. Confounding bias was the main risk of bias in these studies (Table 1, Supplementary Table S5).

Pooled random-effects estimate and publication bias

The estimates of CFR varied from 0% to 63·0% in different geographical regions (Fig. 2). Substantial heterogeneity was observed ($P < 0·001$). For pregnant women with AVH, the pooled random-effects CFRs for maternal and fetal outcomes were 20·8% (95% CI 16·6–25·3) and 34·2% (95% CI 26·0–43·0), respectively (Tables 2, 3, Figs 2, 3). Although the Egger and Begg tests did not suggest the presence of publication bias ($P > 0·05$), the funnel plot produced was asymmetrical.

Subgroup analysis, sensitivity analysis, and meta-regression analysis were used to explore the source of the heterogeneity observed between studies.

Subgroup analysis

Table 2 shows the pooled CFRs of pregnant women in community-based surveys were all lower than those in hospital-based surveys according to different subgroup analysis. The pooled CFR in community-based surveys (12·2%) was significantly lower than that in hospital-based surveys (25·8%) as a whole. The pooled CFR declined gradually over the investigation period (13·4–9·5%) based on the community survey, while it showed an increasing tendency on the hospital survey (22·7–29·4%). The pooled CFRs in the Asian population were all higher than in the African population. Among hospital studies, the estimated CFR was the highest in pregnant women with FHF (61·2%), and 0% in those without FHF. Subgroup analysis of the HEV epidemic demonstrated that outbreak patients had a higher CFR than sporadic ones based on community surveys. Noticeably, the pooled CFR in the third trimester of pregnancy was markedly higher than that in other stages (21·3% and 1·9%), by both community and hospital surveys ($P < 0·05$).

Table 3 shows that most of the fetal pooled CFR in community-based surveys was lower than that in hospital-based surveys according to different subgroup analysis. Different from the comparison of pregnant women, fetal pooled CFR in the Asian population (21·4%) was lower than that in the African population (57·1%) based on the community survey; fetal pooled CFR for the period from 2006 to 2014 was higher than that of other periods. Intrauterine fetal mortality (27·0%) was obviously higher than neonatal mortality (3·9%) in pregnant women infected with HEV ($P < 0·05$).

Sensitivity analysis

The pooled estimates yielded similar results to the original analysis after the removal of any one study (data not shown), and the estimated CFR changed from 20·0% to 22·0%. The removal of 29 smaller subpopulations caused the original estimate to change from 21·7% to 24·9% (Supplementary Table S6).

Meta-regression analysis

Univariate analysis showed that hospital-based surveying ($P = 0·007$) was significantly associated with CFR (Tables 2 and 3). Furthermore, all cases of FHF were reported in the hospital setting. Hospital-based surveying ($P = 0·001$) was the covariate that most significantly affected CFR after adjusting for other factors, i.e. period of investigation, geographical region, study design, and risk of bias.

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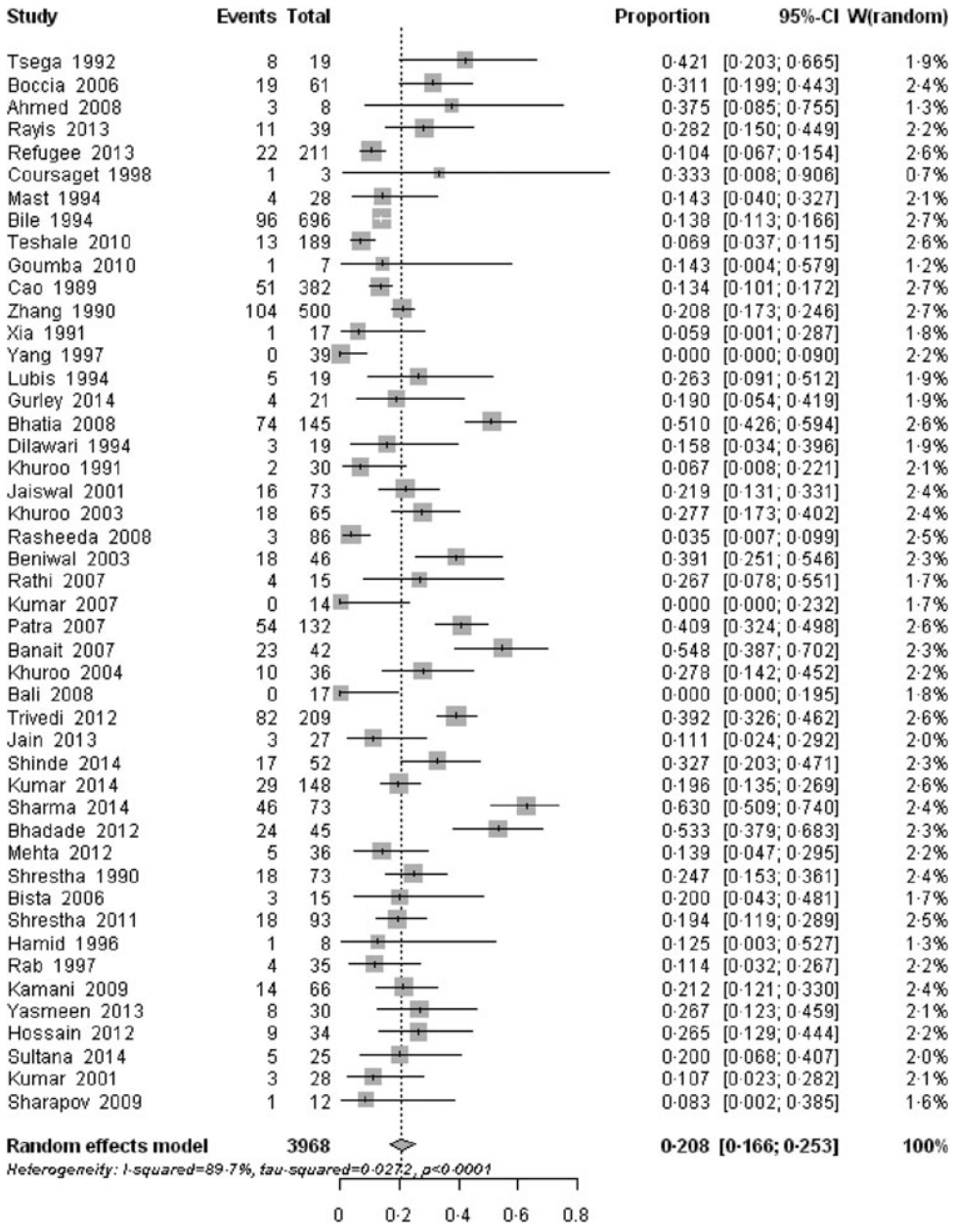

Fig. 2. Forest plot of the case-fatality risk of pregnant women with acute viral hepatitis E, 1986–2014 (included studies are described in the Supplementary material).

DISCUSSION

Our systematic review and meta-analysis of acute viral hepatitis associated with HEV in pregnant women demonstrated the pooled CFRs of maternal and fetal outcomes were 20·8% (95% CI 16·6–25·3) and 34·1% (95% CI 26·2–42·4), respectively. This suggested that in endemic areas, AVH associated with HEV could be a major cause of maternal and fetal death [2]. The study showed that patients in the third trimester of pregnancy had a higher CFR than those in other stages, and intrauterine fetal mortality (27·0%) was statistically higher than neonatal mortality (3·9%) in patients infected with acute hepatitis E. This is due to the fact that acute hepatitis E infection is more common in the third trimester of pregnancy and worsening maternal condition necessitates pregnancy termination, which results in intrauterine fetal death or premature births. However, it is not well understood if the increase in stillbirths is attributable to vertically transmitted infection, or if it is the

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Table 2. *Subgroup analysis and univariate analysis of case-fatality risk of pregnant women with acute viral hepatitis E*

	Community ($n = 16$)			Hospital ($n = 31$)			Total ($n = 47$)		
Variable	Pooled CFR (%)	95% CI	*P* value	Pooled CFR (%)	95% CI	*P* value	Pooled CFR (%)	95% CI	*P* value
All studies*	12·2	9·2–15·6	0·001	25·8	20·1–32·0	<0·001	20·8	16·6–25·3	0·001
Investigation period			**0·730**‡			**0·358**‡			**0·173**‡
1986–1995	13·4	11·6–15·4	0·116	22·7	12·9–34·4	<0·001	17·7	12·5–23·5	<0·001
1996–2005	10·9	0·5–32·3	<0·001	23·4	10·3–39·7	<0·001	19·2	9·3–31·5	<0·001
2006–2014	9·5	5·7–14·0	0·002	29·4	21·2–38·4	<0·001	25·3	17·1–34·4	<0·001
Study design			**0·925**‡			**0·410**‡			**0·190**‡
Retrospective	12·6	8·3–17·7	0·003	22·9	16·1–30·5	<0·001	18·2	13·4–23·5	<0·001
Prospective	11·1	6·7–16·4	0·044	29·0	19·0–40·1	<0·001	24·7	17·0–33·4	<0·001
Area			**0·317**‡			**0·493**‡			**0·985**‡
Asia	13·6	8·7–19·4	0·001	33·2	22·7–44·7	0·761	20·8	16·6–25·3	<0·001
Africa	10·9	6·9–15·8	0·096	24·9	18·9–31·5	<0·001	18·3	12·5–24·9	<0·001
Risk of bias			**0·528**‡			**0·156**‡			**0·617**‡
Moderate	11·4	5·4–41·9	—	34·4	8·5–66·9	<0·001	29·6	9·7–55·0	<0·001
High	12·0	8·9–15·4	0·001	29·1	23·9–34·6	0·001	19·9	15·8–24·3	<0·001
Very high	—	—	—	20·7	11·0–32·5	<0·001	20·7	11·0–32·5	<0·001
Serious disease†						**<0·001**‡			**<0·001**‡
Yes (FHF)	—	—	—	61·2	50·3–72·0	<0·001	61·2	50·3–72·0	<0·001
No (non-FHF)	—	—	—	0·0	0·0–0·2	0·873	0·0	0·0–0·2	0·873
Epidemics			**0·818**‡			**0·095**‡			**0·053**‡
Outbreak	12·4	9·2–16·0	<0·001	21·8	18·6–25·1	0·6391	14·8	11·4–18·6	<0·001
Sporadic	10·0	2·7–21·0	0·814	25·8	19·0–33·2	<0·001	24·6	18·2–31·8	<0·001
Gestation§			**<0·05**‡			**<0·001**‡			**<0·001**‡
Third trimester	12·9	5·4–23·0	0·664	23·2	16·5–30·6	0·001	21·3	15·7–27·6	0·002
Non-third trimester	0·0	0·0–1·8	1·000	2·8	0·5–7·0	<0·001	1·9	0·2–5·3	<0·001

CFR, Case-fatality risk; CI, confidence interval; HEV, hepatitis E virus; FHF, fulminant hepatic failure.

* When CFR was compared between community and hospital, the *P* value was 0·007.

† FHF and non-FHF could not be classified in community-based survey.

‡ *P* value was calculated on the basis of the univariate analysis; other *P* values were calculated on the basis of the analysis of heterogeneity.

§ The numbers of included studies are three in the community and 11 in hospital.

result of maternal complications related to hepatitis E [4, 11]. Some studies indicate that the severity of HEV infection in mother and baby may be closely related, and that fetal disease influences the course of maternal HEV infection [12].

We explored some potential sources of the heterogeneity observed between the analysed studies. First, hospital-based studies may overestimate the CFR of pregnant women with AVH [11]. This is supported statistically by our meta-analysis results, whether they were derived from univariate analysis or multiple variable meta-regressions. More importantly, in the subgroup analysis, the highest CFR associated with HEV occurred in pregnant women with FHF (61·2%) based on hospital reports, which was three times higher than the rate found in all AVH cases. The possible reason is that the former would tend to capture the more severe cases (such as FHF), while mild cases are rarely seen in hospitals. Moreover, the designs of the different studies might have affected the CFR. The pooled estimate of prospective studies yielded higher CFRs than retrospective or cross-sectional studies, although there were no statistically significant differences between these different study types. The possible explanation for this is that retrospective and cross-sectional studies passively collected specimens and failed to detect IgM to HEV and/or HEV RNA in time, and therefore missed more cases than prospective studies. In addition, the CFR of pregnant women with AVH in Asia is higher than for pregnant women in Africa. This may be an example of publication bias, which means only papers

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Table 3. *Subgroup analysis and univariate analysis of fetal case-fatality risk of pregnant women with acute viral hepatitis E*

	Community ($n = 6$)			Hospital ($n = 21$)			Total ($n = 27$)		
Variable	Pooled CFR (%)	95% CI	*P* value	Pooled CFR (%)	95% CI	*P* value	Pooled CFR (%)	95% CI	*P* value
All studies*	23·4	15·9–31·8	0·332	36·6	26·8–47·0	0·000	34·2	26·0–43·0	0·000
Investigation period			**0·289**†			**0·501**†			**0·507**†
1986–1995	22·5	13·6–32·8	0·818	22·7	11·7–36·1	<0·001	22·1	14·2–31·1	0·001
1996–2005	31·3	1·9–75·3	0·026	53·4	31·9–74·2	<0·001	47·5	27·6–67·8	<0·001
2006–2014	28·6	11·8–49·2	—	35·3	27·4–43·6	0·001	34·8	27·4–42·5	0·002
Study design			**0·409**†			**0·035**†			**0·041**†
Retrospective study	24·4	12·0–39·5	0·132	27·9	18·9–37·9	<0·001	27·1	19·6–35·3	<0·001
Prospective study	24·1	13·7–36·2	0·778	45·7	32·9–58·8	<0·001	42·1	30·5–54·2	<0·001
Area			**0·093**†			**0·163**†			**0·191**†
Asia	21·4	14·6–29·2	0·135	37·5	26·4–49·3	<0·001	33·9	24·8–43·7	<0·001
Africa	57·1	21·9–88·7	—	33·3	22·7–44·8	0·009	35·4	25·1–46·4	0·020
Risk of bias			**0·413**†			**0·402**†			**0·450**†
Moderate	28·6	11·8–49·2	—	37·2	29·6–45·1	—	36·1	29·0–43·4	0·432
High	22·7	14·0–32·8	0·253	42·2	27·2–58·0	<0·001	36·8	24·9–49·7	<0·001
Very high	—	—	—	29·9	18·6–42·7	<0·001	29·9	18·6–42·7	<0·001
Epidemics			**0·237**†			**0·304**†			**0·202**†
Outbreak	25·9	17·8–35·0	0·425	24·4	8·8–44·7	0·008	25·3	16·7–35·1	0·010
Sporadic	14·3	4·0–29·4	—	38·4	28·4–48·8	<0·001	36·9	27·3–47·2	<0·001
Death stage‡			**0·024**†			**<0·001**†			**<0·001**†
Intrauterine death	16·4	9·5–24·8	0·237	29·7	20·5–39·9	<0·001	27·0	19·4–35·3	<0·001
Neonatal death	4·6	0·7–11·8	0·053	3·7	1·5–6·8	<0·001	3·9	1·8–6·6	<0·001

CFR, Case-fatality risk; CI, confidence interval; HEV, hepatitis E virus.

* When CFR was compared between community and hospital, the *P* value was 0·069.

† *P* value was calculated on the basis of the univariate analysis; other *P* values were calculated on the basis of the analysis of heterogeneity.

‡ The numbers of included studies are five in the community and 20 in hospital.

describing outbreaks or studies with large fatality rates would be published. By contrast, it is worth noting that fetal mortality in Asia (21·4%) was distinctly lower than in Africa (57·1%) based on community surveys. It may be closely related to the economic level and medical conditions in two regions.

The meta-analysis performed in this study has a number of limitations. First, most of the included studies were conducted in highly endemic areas, including Asia and Africa. Nevertheless, distinct epidemiological patterns are clearly distinguished in endemic regions compared to non-endemic areas. Hepatitis E is a waterborne infection caused by HEV genotype 1, essentially, or genotype 2 in developing countries, while autochthonous hepatitis E is a zoonotic infection caused by HEV genotypes 3 and 4 in developed countries. Most of included studies reported have been associated with focally contaminated drinking water infected by HEV genotypes 1 or 2. The studies can therefore not be assumed to represent cases with other genotypes reported circulating in other, less endemic areas, because no evidence was shown that the zoonotic genotypes (hepatitis E genotypes 3 and 4) were associated with infections in pregnant women or with poor outcomes. Second, the diagnosis of HEV is likely to remain incomplete. Acute HEV infection is usually diagnosed by detecting specific anti-HEV antibodies. All of the included studies described the diagnosis of HEV but used various tests, such as serological or RNA-based detection. Performing the available assay techniques in different settings has been shown to lead to the misclassification of patients infected with HEV [2, 7, 13]. Misclassification of HEV infection because of barriers to medical care, failure to consider hepatitis E in differential diagnosis [11], or the use of insensitive assays may obscure the impact of HEV on pregnancy outcomes. Moreover, the potential differences between sporadic cases and outbreaks of AVH are also important in estimating CFR. An outbreak of

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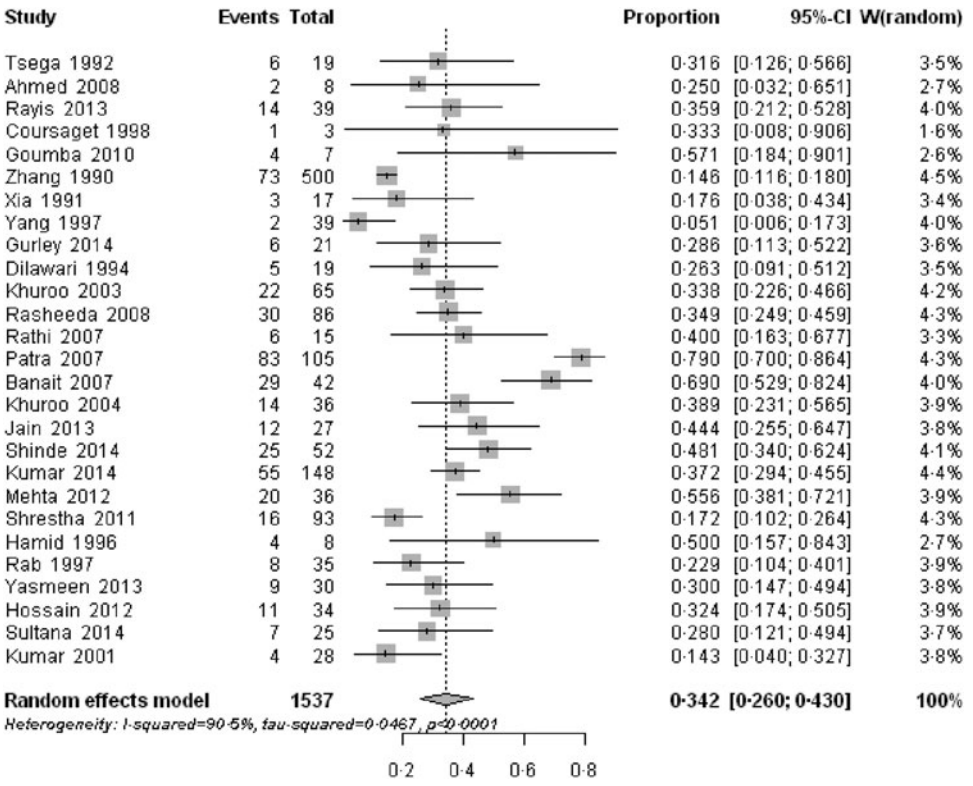

Fig. 3. Forest plot of fetal case-fatality risk of pregnant women with acute viral hepatitis E, 1986–2014 (included studies are described in the Supplementary material).

hepatitis E is more strongly indicated if it is followed by a steep increase in the number of jaundiced pregnant women admitted to hospitals and higher rates of premature deliveries, miscarriages, and stillbirths. Preferential reporting of severe cases during either disease surveillance or cohort studies neglects mild or asymptomatic infections that are less likely to be fatal. This bias leads to an overestimation of CFR [5, 14]. In addition, the study populations assessed in the literature have been largely hospital-based and skewed towards women with more severe illness, a group who have a predisposition for worse fetal and/or neonatal outcomes. Nonetheless, results from the largest prospective studies of women with hepatitis E paint a picture of relatively poor pregnancy outcomes, even in women with milder illness rather than just in those with acute liver failure [15, 16].

Owing to the growing public health concern surrounding AVH caused by HEV in pregnant women in many countries, an international surveillance system is urgently needed to assess the disease burden of pregnant women with AVH. In addition, a direct and effective measure, such as a novel vaccine, is needed to control and prevent the occurrence of AVH in pregnant women. The world's first hepatitis E vaccine, Hecolin (Xiamen Innovax Biotech, China), was approved by China's State Food and Drug Administration in December 2011 after a phase-III clinical trial was published in 2010 [17]. Preliminary evidence has suggested that the Hecolin vaccine is safe for use in pregnant women [18]. However, these findings should be confirmed in larger future studies.

In conclusion, to reduce the disease burden of AVH associated with HEV, an international surveillance network should be established to evaluate the distinct geographical regions affected by the disease. Furthermore, vaccines against HEV should be developed to control AVH caused by HEV in pregnant women.

SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0950268816000418.

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DECLARATION OF INTEREST

None.

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