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REVIEW

Prenatal alcohol exposure and offspring liver dysfunction: a systematic review and meta-analysis

Qunying Liu[1,2] · Fengyu Gao[3] · Xiangrong Liu[4] · Jing Li[5] · Yan Wang[2] · Jun Han[2] · Xietong Wang[1]

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Abstract
Purpose Limited studies have reported the effect of prenatal alcohol exposure (PAE) on fetal liver development or liver dysfunction. The current review was conducted to systematically review published studies of PAE and liver dysfunction.
Methods Pub Med, Embase and Web of Science database were searched using terms of "prenatal alcohol exposure" and "liver" or "fetal alcohol spectrum disease" and "liver". The pooled effect size of alcohol exposure was assessed by Hedges's g and 95 % confidence interval (CI) using fixed model or random model depending on the heterogeneity determined by Q test and I^2 statistic.
Results A total of 23 studies were included. The results indicated that gestation alcohol exposure resulted in significant reduction of fetal body weight (Hedges's $g = -6.854 \pm 1.149$, 95 % CI -9.106 to -4.602, $P < 0.001$), but not fetal liver weight reduction (Hedges's $g = -0.076 \pm 0.878, 95\ \%\ \text{CI}\ -1.799$ to $1.647, P = 0.931$). PAE resulted in significant decline in protein synthesis or enzyme activity of offspring fetal liver including glutathione and $25(OH)_2D$ (Hedges's $g = -1.149 \pm 0.108$, 95 % CI -1.361 to -0.938, $P < 0.001$), as well as significant increase in proteins including oxidants and collagen (Hedges's $g = 1.330 \pm 0.146$, 95 % CI 1.044–1.616, $P < 0.001$).
Conclusion These results suggested that PAE affects fetal body weight but not liver weight, and that PAE may result in offspring fetal liver dysfunction.

Keywords Prenatal alcohol exposure · Liver dysfunction · Systematic review · Meta-analysis

Introduction

A major cause of birth defects today is maternal consumption of alcohol. Prenatal alcohol exposure (PAE) may have various kinds of adverse effects on the offspring fetus including congenital heart disease, growth deficiency, central nervous dysfunction, and abnormal liver function [1–4]. All these adverse effects of PAE on fetal development are collectively called fetal alcohol syndrome (FAS) or fetal alcohol spectrum disorder (FASD).

Currently, effect of prenatal alcohol exposure (PAE) on central nervous system dysfunction and growth deficiency has been extensively studied in human beings. In contrast, studies on PAE and liver dysfunction are limited and there is a lack of prospective cohort study on this topic. Instead, based on the database search including PubMed, Embase, and Web of Science, studies published to date on prenatal alcohol exposure and aberrant liver function or liver development were carried out in animal models only. The current review is, therefore, designed to systematically search public database and analyze the effect of prenatal

✉ Xietong Wang
xietongwangqingdao@126.com

1 Department of Obstetric and Gynecology, Shandong Provincial Hospital Affiliated to Shandong University, 324 Jingwu Road, Jinan 250021, Shandong, China

2 Department of Obstetrics, Eighth People's Hospital of Qingdao, Qingdao 266100, Shandong, China

3 Department of Gastroenterology, Qingdao Hiser Medical Group, Qingdao 266033, Shandong, China

4 Department of Internal Medicine, Qingdao Women and Children Hospital, Qingdao 266000, Shandong, China

5 Department of Obstetric and Gynecology, The Affiliated Hospital of Qingdao University, Qingdao 266000, Shandong, China

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(or gestation) alcohol exposure on fetal liver function of protein synthesis and enzyme activity.

Materials and methods

Data sources

This systematic review followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) criteria [5]. Relevant literature was searched in the sites of PubMed, Embase, and Web of Science with the following phrases: "prenatal alcohol exposure" and "liver", or "fetal alcohol spectrum disorders" and "liver". The search was limited to English.

Inclusion criteria

Studies were included in the current systematic review if: (1) studies on the effect of prenatal alcohol exposure (PAE) or fetal alcohol spectrum disorders (FASD) on fetal liver weight and body weight in animals; (2) studies on the effect of PAE or FASD on alteration of liver enzyme activity, protein synthesis or mRNA expression; (3) studies on the effect of PAE or FASD on structural or functional alteration of liver cells including apoptosis or necrosis; (4) studies with full-text articles.

Data extraction

Information and data were carefully extracted from all included literature according to the inclusion criteria as aforementioned. Data include study name (the first author name), publication date, study design, total number of cases or replications of the experiment, and parameters of liver function.

Statistical analysis

The following forms of data were used for the data entry: (1) mean, standard deviation (SD), number of cases or replications; (2) sample size of alcohol exposure, sample size of control, and P value of comparison between the two groups. The strength and contribution of maternal alcohol exposure to alteration of offspring liver function were measured by Hedges's g. A fixed effect model was adopted when no heterogeneity was observed among the studies. Otherwise, a random effect model was applied. The heterogeneity between studies was assessed by the Q test and I^2 statistic, and $P < 0.10$ and $I^2 > 50$ % were considered as heterogeneous between the studies [6]. All meta-analyses were performed using the Comprehensive Meta-analysis software (Version 3, NJ, USA).

Results

Study features

The process of selecting literature was outlined as in Fig. 1. After careful reading of "abstract" of publications, total 45 full-text articles were retrieved. The retrieved full-text articles were then independently assessed by two investigators. As shown in Table 1, 23 articles were finally included in the current systematic review [3, 7–28]. All studies were carried out in animals, and majority of them (18 articles) were studied in rat, two were in guinea pigs, two were in mice (C57BLK/6J), and one was studied in ewes. Protocol of maternal exposure alcohol was varied, and concentration of alcohol also varied from 5 to 25 % (v/v) or 2 to 6 g/kg body weight. Twelve studies measured fetal body weight and nine studies measured fetal liver weight. Among the 23 articles, 12 articles were from USA, 5 from Canada, 5 from Spain, 1 from Italy, and 1 from UK.

PAE effect on body weight and fetal weight

Twelve out of the 23 studies included in the current review studied the effect of PAE on fetal body weight, and 9 out of the 23 publications studied the effect of PAE on fetal liver weight. When the overall effect size of PAE on fetal body weight and liver weight was pooled into the meta-analysis, random effect model was used, so that there was heterogeneity among the studies ($I^2 = 97.7$, $P < 0.01$). As shown in Fig. 2, there was statistically significant inhibitory effect of PAE on

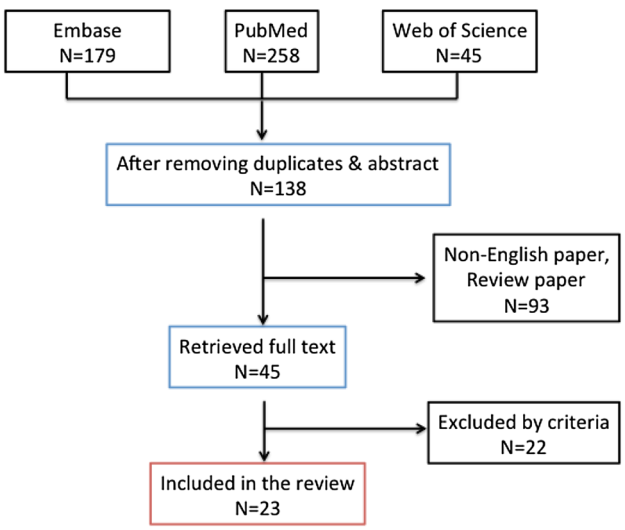

Fig. 1 Flow diagram of literature search and eligible publication selection

Table 1 Summary of the included *s*tudies

First author	Year	Country	Animal	EOH exposure	Fetal wt	Liver wt	Liver parameters
Milne	1985	USA	Rat	20 % on gd 6	Y		Liver 25(OH)2D
Witek-Janusek	1986	USA	Rat	6 % on gd 0	Y		Glucose, glycogen
Harris	1990	USA	Rat	12–36 % gd 0		Y	Protein, zinc, metallothionein
Reyes	1992	USA	Rat	35 % EDC gd 0	Y	Y	GSH
Mauceri	1994	USA	Rat	6.6 % gd 0	Y		ICF-II
Burdge	1995	UK	Guinea pig	6 g/kg gd 0	Y		PC, PE
Marin-Garcia	1996	USA	Rat	36 % of calories	Y	Y	Complex I, III, IV, V
Addolorato	1997	Italy	Rat	20 % gd 14–19		Y	GSH
Renau-Piqueras	1997	Spain	Rat	5 % gd		Y	Con A, Anti-β-COP, GAF1, GAF2
Grange	1999	USA	Rat	6.7 % gd	Y	Y	GGTP activity
Edwards	2000	USA	Rat	6.7 % gd	Y		GGTP activity
Robinson	2002	USA	Rat	6 % gd	Y	Y	B, T and NK cell number
Garcia-Rodriguez	2003	Spain	Rat	5–20 % gd			Anti-DNPH, anti-EF-2
Chen	2004	Canada	Rat	2 g/kg	Y		Triglycerides
Arorin	2004	Spain	Rat	?			Albumin, hepatocyte tubulin
Nammi	2006	Canada	Rat	2 g/kg			Corticorsterone, 11β-HSD1 reductase
Yao	2008	Canada	Rat	2 g/kg			HDAC activity, HAT, HDAC1 protein
Luisa Ojeda	2009	Spain	Rat	?	Y		Liver selenium, GSH
Hewitt	2009	Canada	Guinea pig	20 % gd			CYP2E1
Murillo-Fuentes	2010	Spain	Rat	5–20 % gd		Y	Zinc level
Drver	2012	USA	C57BL/6J	?	Y		8-OHG, SOD, GPx, CAT
Sozo	2013	Canada	Ewes	0.75 g/kg gd		Y	Collagen, ferric iron, hepcidin, cytokines
Hill	2013	USA	C57BL/6J	25% gd 8, IP			NOX isoforms

gd gestation day, *EDC* ethanol derived calories, *IP* intraperitoneal injection, *PC* phosphatidylcholine, *PE* phosphatidylethanolamine, *Con A* concanavalin A, *β-COP* β-coatomer protein, *GAF* Golgi apparatus fraction, *GGTP* gamma glutamyl transpeptidase, *DNPH* 2,4-dinitrophenyl-hydrazine, *11β-HSD1* 11β-hydroxysteroid dehydrogenase type I, *HDAC* histone deacetylase, *HAT* histone acetyltransferase, *CYP2E1* cytochrome P450 2E1, *8-OHC* 8-hydroxyguanosine, *SOD* superoxide dismutase, *GPx* glutathione peroxidase, *CAT* catalase, *NOX* NADPH oxidase

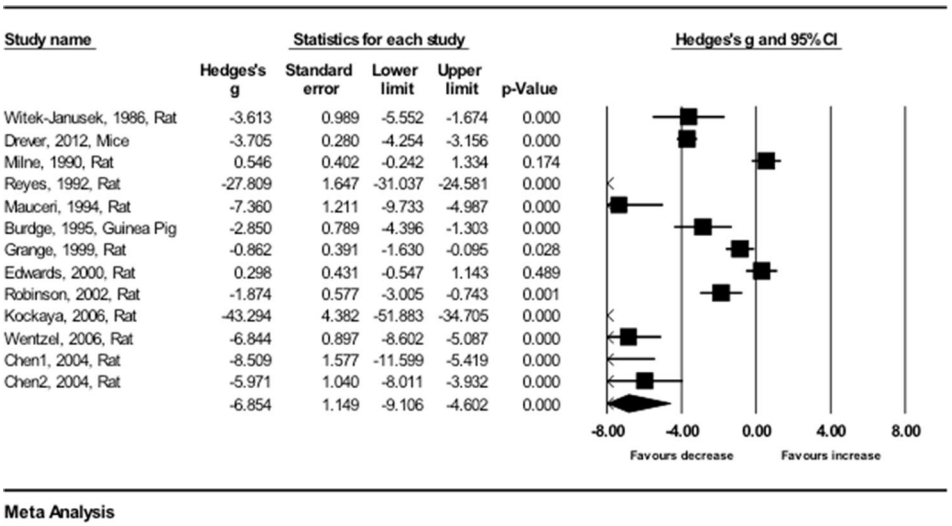

Fig. 2 Forest plot for fetal body weight. A random effect model was used due to significant heterogeneity of publications ($I^2 = 97.7$, $P < 0.01$). Effect size was assessed by Hedges's g and 95 % CI, and the effect of prenatal alcohol exposure was in favor of decreasing fetal body weight (Hedges's $g = -6.854 \pm 1.149$, 95 % CI: -9.106 to -4.602, and $P < 0.001$)

offspring fetal body weight, effect size (Hedges's g) was -6.854 ± 1.149, 95 % CI: -9.106 to -4.602, and $P < 0.001$. However, there was no significant inhibitory effect of PAE on offspring liver weight, effect size (Hedges's g) was -0.076 ± 0.878, 95 % CI: -1.799 to 0.879, and $P = 0.931$ (Fig. 3).

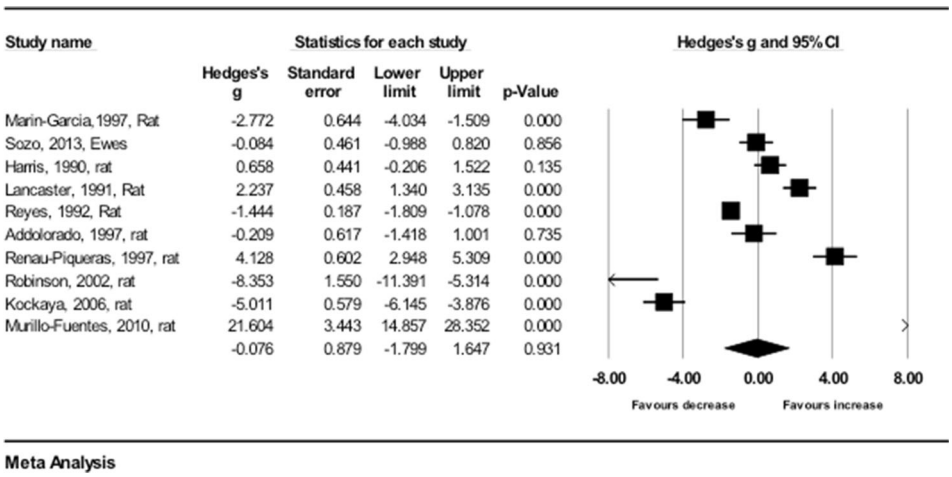

Fig. 3 Forest plot for fetal liver weight. A random effect model was used due to significant heterogeneity of publications ($I^2 = 96.6$, $P < 0.01$). Effect size was assessed by Hedges's g and 95 % CI, and the effect of prenatal alcohol exposure on fetal liver weight was slightly in favor of decreasing fetal liver weight, but it was not statistically significant (Hedges's $g = -0.076 \pm 0.879$, 95 % CI: -1.79 to 1.647, $P = 0.931$)

PAE effect on liver protein synthesis and enzyme activity

Next, effect size of prenatal alcohol exposure on liver protein synthesis or enzyme activity was assessed. In response to alcohol stimulation, proteins that are harmful to fetal health or liver function are expected to be upregulated, and in contrast, proteins that are necessary for normal fetal growth and liver function are expected to be downregulated. Thus, proteins or enzymes were analyzed separately by grouping into two groups. Proteins that are expected to decrease in response to alcohol include $25(OH)_2D$, metallothionein, glutathione (GSH), phosphatidylcholine, ATP synthases, and histone acetyltransferase (HAT) etc. In contrast, proteins that are expected to increase in response to alcohol include gamma glutamyl transpeptidase (GGTP), oxidants such as 2,4-dinitrophenylhydrazine (DNPH), triglycerides, liver albumin, corticorsterone, 11ß-hydroxysteroid dehydrogenase type I (11ß-HSD1), histone deacetylase (HDAC), collagen, ferroportin, NADPH oxidase (NOX), and inflammatory cytokines.

When the overall effect size of PAE on liver protein synthesis and enzyme activity was pooled into the meta-analysis, a fixed effect model was adopted in assessing the effect size of PAE on offspring fetal liver protein or enzyme alteration in that the heterogeneity was very low (Q value $= 11.102$, $I^2 < 0.001$, $P = 0.944$). Suppressive effect size of PAE on liver protein synthesis and enzyme activity was statistically significant (Hedges's $g = -1.149 \pm 0.108$, 95 % CI: -1.361 to -0.938, $P < 0.001$, Fig. 4), which included $25(OH)_2D$, metallothionein, glutathione (GSH), phosphatidylcholine, ATP synthases complex III and V, and histone acetyltransferase (HAT) etc. Similarly, a fixed model was used in assessing the stimulatory effect size of PAE on fetal liver protein synthesis and enzyme activity due to very low heterogeneity (Q value $= 9.212$, $I^2 < 0.001$, $P = 0.757$). The effect size was also statistically significant (Hedges's $g = 1.330 \pm 0.146$, 95 % CI: 1.044–1.616, $P < 0.001$), which included GGTP, oxidants such as DNPH, triglycerides, liver albumin, corticorsterone, 11ß-HSD1, HDAC, collagen, ferroportin, NOXs, and inflammatory cytokines.

Discussion

Fetal alcohol syndrome (FAS) or fetal alcohol spectrum disease (FASD) is the gestation alcohol consumption related consequence. The prevalence of fetal alcohol syndrome (FAS) is highest among children born to Native Americans (0.3 % of live birth), followed by African Americans (0.06 %), whites (0.009 %), and Hispanics (0.008 %), with the lowest rate among Asian Americans (0.003 %) [29]. No single threshold level of alcohol consumption has been associated with the development of FAS, probably owing to differences in fetal vulnerability to the toxic effects of alcohol. While damage of central nervous system is most extensively studied in FASD, aberrant liver development, however, is less extensively studied. In this regard, currently available data of maternal alcohol consumption and its contribution to abnormal fetal liver development are limited in animal studies only. Therefore, studies included in the current review are limited in animal studies, and this is one of the limitations of the current review. Nevertheless, we were able to include 23 animal studies, which demonstrated that prenatal alcohol exposure caused alteration of liver protein synthesis or enzyme activity (Fig. 5).

Most of the studies included in this review were carried out in rats by feeding the pregnant animals with 5–25 % alcohol (v/v) from day 0 of gestation. Protocol of gestation alcohol exposure varies between the studies and whether the amount of alcohol exposure is close to human

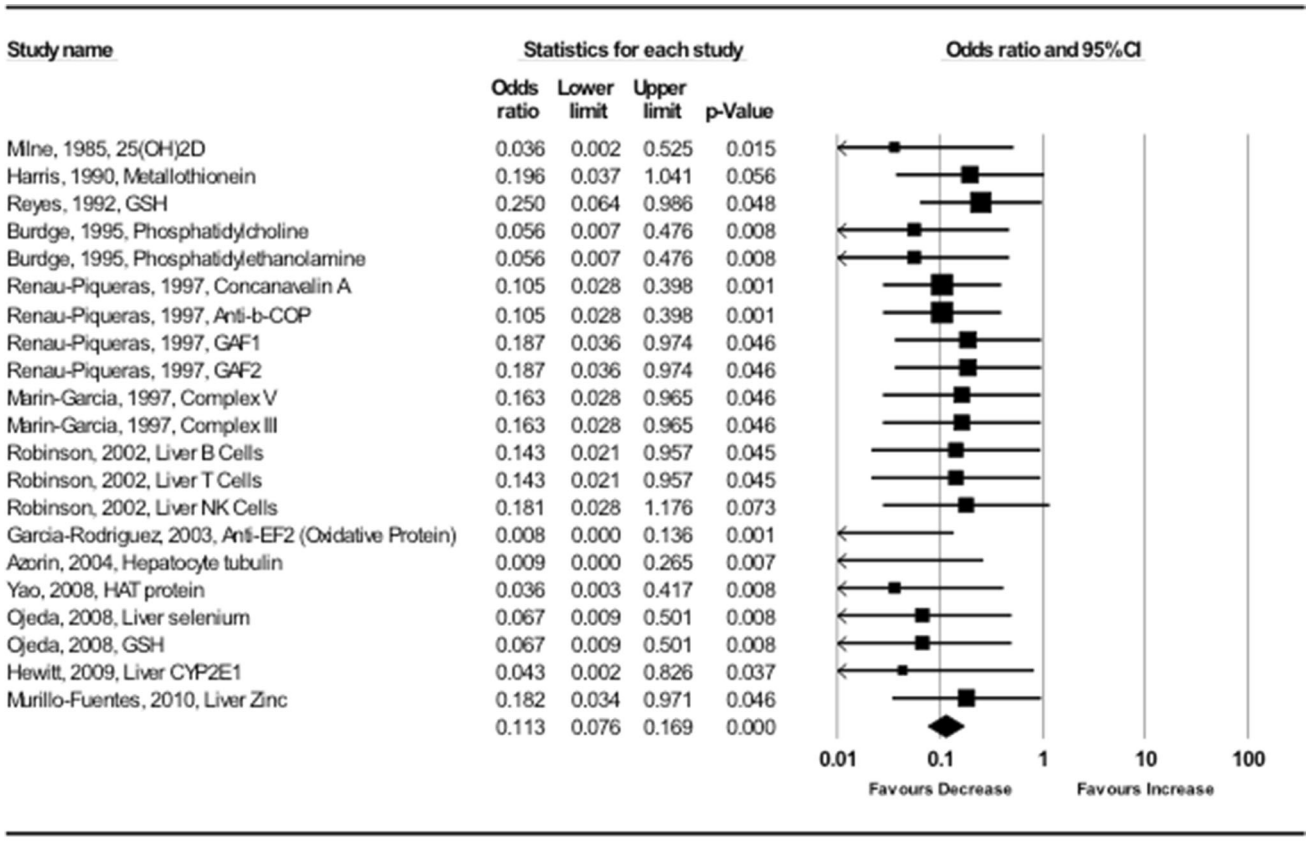

Fig. 4 Forest plot for "down-regulated" proteins in fetal liver. A fixed effect model was used in that no heterogeneity of publications was observed ($I^2 < 0.001$, $P = 0.944$). Effect size was assessed by Hedges's g and 95 % CI, and the effect of prenatal alcohol exposure on synthesis of the fetal liver proteins of this group was in favor of decreasing and was statistically significant (Hedges's $g = -1.149 \pm 0.108$; 95 % CI: -1.361 to -0.938, $P < 0.001$)

consumption remains to be defined. However, systematic review of the 23 articles indicated that prenatal alcohol exposure results in reduction in fetal body weight, but not liver weight.

In response to gestation alcohol exposure, some proteins may be downregulated, while some proteins may be upregulated. Thus, effect of prenatal alcohol exposure on fetal liver protein synthesis or enzyme activity was analyzed by grouping them into "down-regulation" and "up-regulation" groups. "Down-regulation" group included anti-oxidants (glutathione), $25(OH)_2D$, metallothionein, phosphatidylcholine and phosphatidylethanolamine, mitochondrial proteins (complex III and V), histone acetyltransferase (HAT), minerals (selenium and zinc), enzymes (HAT, CYP2E1), and immune cells (B, T, and NK cells). "Up-regulation" group proteins or enzymes included oxidants, glucose or glycogen, inflammatory cytokines, collagen, albumin, triglycerides, and enzymes (GGTP, H6PD).

The biological significance for the proteins included in the current review is known, while some remains to be determined. For instance, synthesis of $25(OH)_2D$ and glutathione in liver is important [30, 31], and immune cells play an important role in liver homeostasis [32, 33]. Inflammatory cytokines involve in mediating chronic inflammation following alcohol exposure [34, 35]. HDAC and HAT activities in liver play an important role in regulating gene expression [36, 37]. Recent studies have examined potential benefits of phosphatidylcholine for liver repair. Results are mixed in animal models [38], and no clinical evidence shows a health benefit in humans. One study shows the healing effect of phosphatidylcholine in mice with hepatitis A, hepatitis B, and hepatitis C. The administration of phosphatidylcholine for chronic, active hepatitis resulted in significant reduction of disease activity in mice [39]. Regardless of the biological functions of aforementioned proteins, the current systematic review demonstrated that prenatal alcohol exposure resulted in significant alteration in fetal liver protein synthesis and enzyme activity.

In summary, the current systematic review included 23 published articles to analyze the effect of gestation alcohol

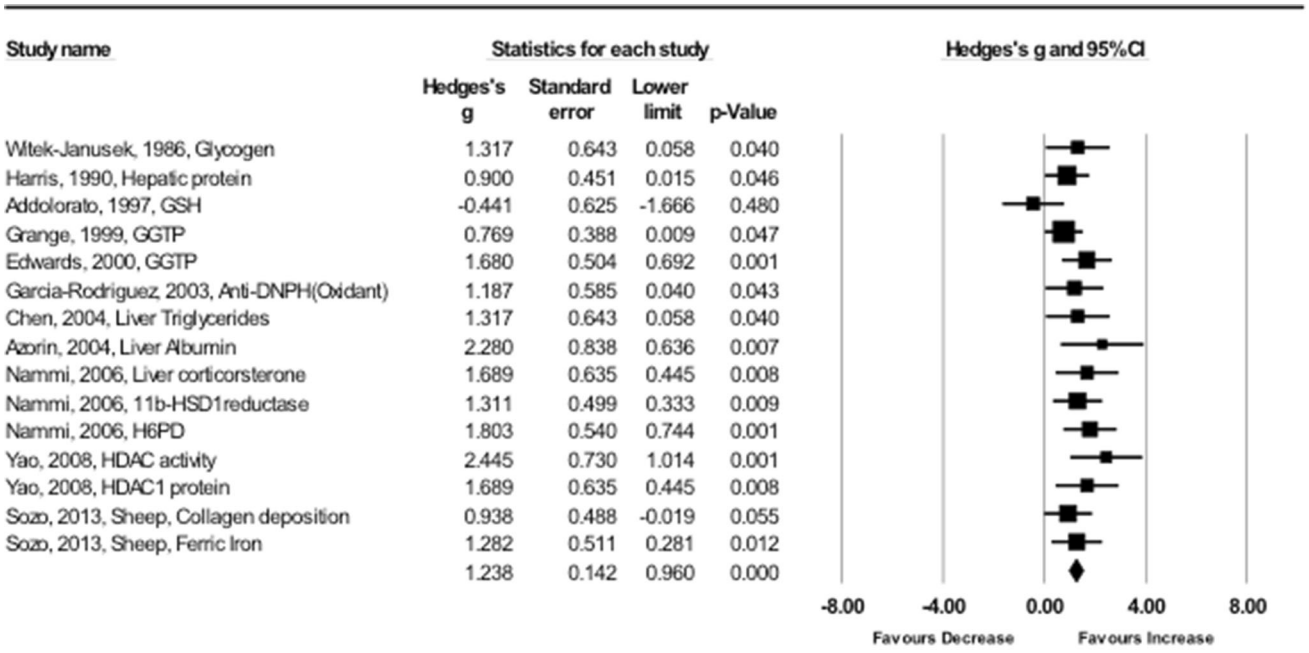

Fig. 5 Forest plot for "up-regulated" proteins in fetal liver. A fixed effect model was used due to the very low heterogeneity of publications ($I^2 < 0.001$, $P = 0.757$). Effect size was assessed by Hedges's g and 95 % CI, and the effect of prenatal alcohol exposure on synthesis of the fetal liver proteins of this group was in favor of increasing and was statistically significant (Hedges's $g = 1.330 \pm 0.146$; 95 % CI: 1.044–1.616, $P < 0.001$)

exposure on offspring fetal liver functions of protein synthesis and enzyme activity. It was found that gestation alcohol exposure had negative effect on fetal body weight, but not significant effect on liver weight. Gestation alcohol exposure in animals resulted in significant alteration of protein synthesis or enzyme activity in offspring fetal liver. Limitation of the current review is the inclusion of animal studies only and clinical cases of prenatal alcohol exposure in pregnant women remain to be studied.

Compliance with ethical standards

Funding There is no funding source for this study.

Conflict of interest All authors declare that there is no conflict of interest.

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