TINJAUAN PUSTAKA — *LITERATURE REVIEW*

Effect of Arsenic Contamination in Drinking Water During Pregnancy with the Incidence of Congenital Heart Disease: A Meta-Analysis

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Abstract

Background: Water is a basic human need. The need for clean water continues to increase along with the increasing human population. Drinking water providers are required to provide harmless water. Several studies have discussed the effect of arsenic contamination in drinking water on the incidence of congenital heart disease. Objective: To evaluate the impact of arsenic contamination in drinking water during pregnancy on the incidence of congenital heart disease. Method: Search for published scientific articles using the PRISMA (Preferred Reporting, Items for Systematic Reviews and Meta-Analysis) method conducted on PubMed using the following keywords: "arsenic", "drinking water" "contamination", "congenital heart desease", "congenital heart defect" as the keyword, also combined by using "or" and "and". Further meta-analysis using Jamovi version 2.2.5 software were performed based on the included published scientific articles. Result: Based on 3 studies included about effect of arsenic contamination in drinking water during pregnancy with the incidence of congenital heart disease, the analytical results showed a statistically significant positive relationship (z=1.42, p<0.001;95% CI[-0.038;0.240]) but in the low category (r=0.101). **Conclusion:** Arsenic contamination in drinking water during pregnancy has a low effect on the incidence of congenital heart disease.

Keyword: drinking water, arsenic, congenital heart disease

INTRODUCTION

In 1973 a study reported the incidence of congenital heart disease which was found in one third of the population of an area called Tuscon Valley in the United States. In 1981 another study found an association between contamination of drinking water sources by trichlorethylene and chromium with the incidence of congenital heart disease in the area.1

In 1988 Zierler et al. conducted a population study on the effect of 11 inorganic chemicals that are thought to affect health based on animal studies. Some of the chemicals thought to be the most influential are arsenic, cadmium, fluoride, and mercury.2 In 2001 WHO released a statement that in animal experiments, several abnormalities caused by arsenic exposure were found, such as fused ribs, renal agenesis, micromelia, facial marfolmation, twisted hindlimbs, anophtalmia, and microphthalmia.3

Arsenic in nature is usually found in association with other elements and forms various compounds. Inorganic arsenic is a component resulting from human activities such as mining, smelting, and industries that use arsenic and pollute the environment. Inorganic arsenic can be found in soil, sediment, and groundwater. People can be exposed to inorganic arsenic through contaminated drinking water and food.4 In 1963 WHO set the maximum arsenic level in drinking water at 50-200 µg/L, in 1993 it was revised to 10-50 µg/L, and in the latest WHO guidelines it recommended arsenic levels below 10 µg/L considering that water treatment and analytical capabilities in some areas were limited. For this reason, WHO recommends the lowest possible arsenic level.5

Several studies were conducted in various countries regarding the effect of arsenic contamination in drinking water at various concentrations. This meta-analysis aims to determine the effect of arsenic contamination during pregnancy on the incidence of congenital heart disease.

METHODS

Database searching

The present analysis was conducted according to with published Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline. We searched PubMed (1 July to 7 August 2022) for a record the effect of arsenic contamination during pregnancy on the incidence of congenital heart disease. Our search terms included: "arsenic", "drinking water" "contamination", "congenital heart desease", "congenital heart defect" as the keyword, also combined by using "or" and "and". Two independent authors performed the search and literature screening (Y.P., A.D.J.N.R, and K.A.A.P.P), with disputes resolved by consensus following discussion with a third author (R.E).

Study selection

Reviewer screened the journal for inclusion based on the following criteria: the study reports the total sample for the control and experimental groups as well as the number of incidents in the control and experimental group, their corresponding 95% confidence intervals (CIs), studies include concentrations of arsenic found in drinking water. The study was excluded if it did not meet the inclusion criteria, and studies that were published in languages other than English.

Data analysis

We performed the analysis using the Jamovi version 2.2.5 software. The heterogeneity of this study was examined by p-value. For p>0,005 indicates low heterogeneity, p<0,005 indicates substantial heterogeneity. and a r =0.1 was considered as low, r=0.3 as medium, and r=0.5 as height category effect.

RESULTS

The primary endpoint is arsenic contamination in drinking water during pregnancy increased the incidence of congenital heart disease. In the PRISMA flow chart, there are 455 studies citation screened and selected 3 studies (including n=1,068,962 participants) (figure 1).

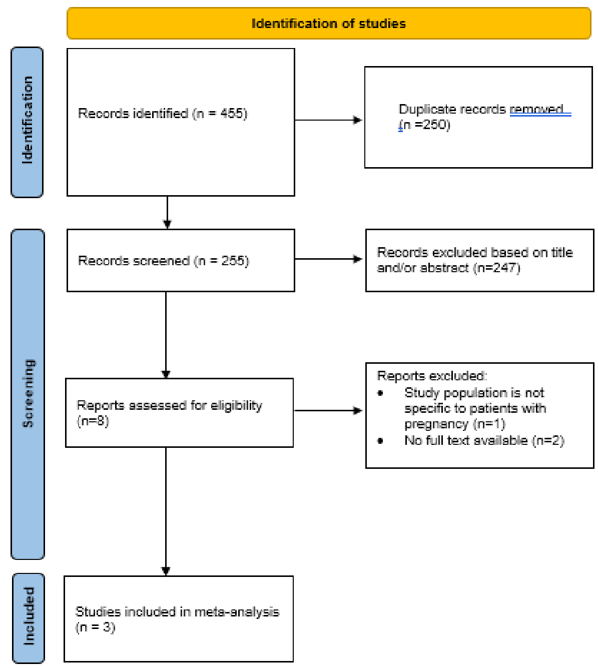

FIGURE 1. PRISMA flowchart

Heterogeneity Statistics

The results of the analysis (table 1) showed that the 10 effect sizes analyzed were heterogeneous (Q=151,985, p<0.001). Thus, the random effects model is more suitable to be used to estimate the mean effect size of the 10 analyzed studies. The results of the analysis also indicate that there is potential to investigate moderating variables that influence the relationship between arsenic contamination in drinking water and congenital heart disease.

Table 1. Heterogeneity Statistics

Tau	Tau²	I²	H²	R²	df	Q	p
0.201	0.0406 (SE= 0.0233)	94.15%	17.095	.	9.000	151.985	<0 .001

Random-Effects Model (k = 10)

The results of the analysis using a random effect model (table 2) showed that there was a significant positive correlation between arsenic contamination in drinking water and congenital heart disease (z=1.42, p<0.001;95% CI[-0.038;0.240]). As for the effect of arsenic contamination in drinking water with congenital heart disease, it is included in the low category (r=0.101), which is r=0.1 (low); r=0.3 (medium); r=0.5 (height). (Cohen, 1988).

Table 2. Random-Effects Model

	Estimate	se	Z	p	CI Lower Bound	CI Upper Bound
Intercept	0.101	0.0709	1.42	0.156	-0.038	0.240
	.	.	.	.	.	.

Note. Tau² Estimator: Restricted Maximum-Likelihood

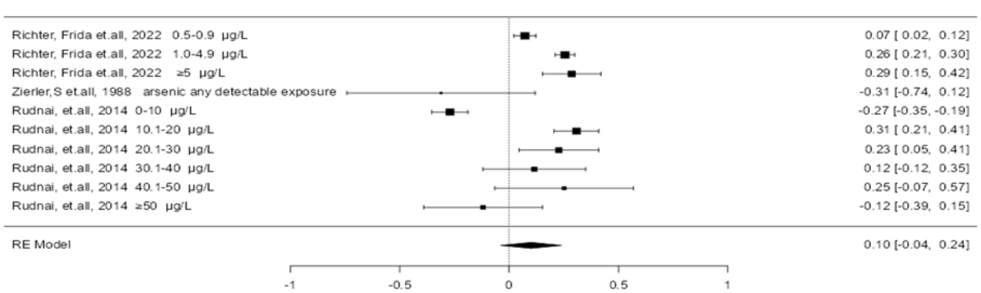

FIGURE 2. Forest plot

From the forest plot (Figure 2), it can be observed that the effect size of the analyzed studies varies from -0.31 to 0.31. Funenl plot (Figure 3) results show symmetrical results.

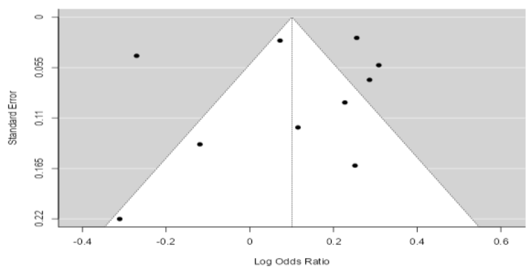

FIGURE 3. Funnel plot

Regression Test for Funnel Plot Asymmetry

Moreover, $p>0.05$ confirms that the funnel plot (Figure 3) is symmetrical. Thus it can be concluded that there is no problem of publication bias in the meta-analysis study.

Table 3. Regression Test

Z	p
-0.834	0.404

Fail-Safe N Analysis (File Drawer Analysis)

Because K=10, so 5K+10=5(10)+10=60. The fail-safe N value obtained is 146, with a target significance of 0.05 and $p<0.001$. Because the value of fail-save N > 5K + 10, it can be concluded that there is no publication bias in the meta-analysis study.

Table 4. Fail-Safe N Analysis

Fail-safe N	p
146.000	< .001

Note. Fail-safe N Calculation Using the Rosenthal Approach

DISCUSSION

his meta-analysis uses three articles that discuss the effect of arsenic contamination in drinking water during pregnancy with the incidence of congenital heart disease. The mechanism for the occurrence of congenital heart disease due to arsenic contamination is still not known with certainty. Some hypotheses suggest that arsenic can enter the placenta and cause disruption of the methylation process and epigenetic action.6,7 A review study conducted by Nicoll, Rachel, 2018 found that several environmental contaminants caused genetic polymorphisms such as genetic variants of transforming growth factor beta (TGF-B) receptor type I (TGFBR1) and type 2 (TGFBR2) which are often found in Marfan syndrome. ductus arteriosus and VSD.8

After the analysis, it was found that there was a significant positive relationship (z=1.42, p<0.001;95% CI[-0.038;0.240]) but in the low category (r=0.101). This is probably because the data on the arsenic content of drinking water differ in each article, ranging from 0.5 - > 50 µg/L. The amount of arsenic in drinking water that varies may affect the effect size of this study because the data in this study are heterogeneous (Q=151,985, p<0.001) so that it is possible that there are moderating variables that can affect the effect size of this study. A study in France can support this opinion, where in the study found that the incidence of congenital anomalies (including congenital heart disease) increased significantly in the group with arsenic exposure > 10 µg/L compared to the group with 1-10 µg/L exposure.9 A case control study by Zierler et al also showed that an early drinking water study had found an association of arsenic with CHD coarctation of the aorta, with OR 3.4 (95% CI: 1.3, 8.9).10

Our meta-analysis also inline with recent Hungarian case control study by Rudnai, et al that investigated nearly 10,000 cases of congenital heart defects and found an association between an arsenic level >10 µg/L (the current EU limit) and total CHD incidence, with OR 1.41 (95% CI: 1.28, 1.56).11 A case control study conducted in China by Jin, et al showed that arsenic concentrations ≥62.03 ng/g were associated with increased risk for almost every CHD subtype (AOR 1.96; 95% CI 1.24–3.09).12 This meta-analysis has several limitations. The included studies were relatively small. Therefore, the results of this study need to be confirmed by a large meta-analysis in the future.

CONCLUSION

Arsenic contamination in drinking water during pregnancy with the incidence of congenital heart disease have significant positive relationship (z=1.42, p<0.001;95% CI[-0.038;0.240]) but in the low category (r=0.101)

DAFTAR PUSTAKA

1.Goldberg, S. J., Lebowitz, M. D., Graver, E. J., & Hicks, S. An association of human congenital cardiac malformations and drinking water contaminants. Journal of the American College of Cardiology. 1990; 16(1): 155–164.

2.Ersbøll, A.K., Monrad, M., Sørensen, M., Baastrup, R., Hansen, B., Bach, F.W., Tjønneland, A., Overvad, K., Raaschou-Nielsen, O. Low-level exposure to arsenic in drinking water and incidence rate of stroke: a cohort study in Denmark. Environ. Int. 2018; 120: 72–80.

3.WHO. Arsenic and Arsenic Compounds. Environmental Healt Criteria 224. Geneva : s.n., 2001.

4.Marie, C., Léger, S., Guttmann, A., Marchiset, N., Rivière, O., Perthus, I., Lémery, D., Vendittelli, F., & Sauvant-Rochat, M.-P. In utero exposure to arsenic in tap water and congenital anomalies: A French semi-ecological study. International Journal of Hygiene and Environmental Health.2018; 221(8): 1116–1123.

5.Ramsay, L., Petersen, M. M., Hansen, B., Schullehner, J., van der Wens, P., Voutchkova, D., & Kristiansen, S. M. Drinking water criteria for arsenic in high-income, low-dose countries: The effect of legislation on Public Health. Environmental Science & Technology.2021; 55(6): 3483–3493.

6.Ahmad, A., van der Wens, P., Baken, K., de Waal, L., Bhattacharya, P., Stuyfzand, P. Arsenic reduction to <1 µg/L in Dutch drinking water. Environ. Int. 2020; 134: 10525.

7.Chen, Y., Graziano, J.H., Parvez, F., Liu, M., Slavkovich, V., Kalra, T., Argos, M., Islam, T., Ahmed, A., Rakibuz-Zaman, M., Hasan, R., Sarwar, G., Levy, D., van Geen, A., Ahsan, H. Arsenic exposure from drinking water and mortality from cardiovascular disease in Bangladesh: prospective cohort study. BMJ. 2011; 342: d2431.

8.Nicoll R. Environmental Contaminants and Congenital Heart Defects: A Re-Evaluation of the Evidence. International journal of environmental research and public health.2018; 15(10): 2096.

9.Richter, F., Kloster, S., Wodschow, K., Hansen, B., Schullehner, J., Kristiansen, S. M., Petersen, M. M., Strandberg-Larsen, K., & Ersbøll, A. K. Maternal exposure to arsenic in drinking water and risk of congenital heart disease in the offspring. Environment international.2022: 160; 107051.

10.Zierler, S.; Theodore, M.; Cohen, A.; Rothman, K.J. Chemical quality of maternal drinking water and congenital heart disease. Int. J. Epidemiol. 1988; 17:589–594.

11.Rudnai, T.; Sándor, J.; Kádár, M.; Borsányi, M.; Béres, J.; Métneki, J.; Maráczi, G.; Rudnai, P. Arsenic in drinking water and congenital heart anomalies in Hungary. Int. J. Hyg. Environ. Health. 2014; 217: 813–818.

12.Jin, X., Tian, X., Liu, Z., Hu, H., Li, X., Deng, Y., Li, N., & Zhu, J. Maternal exposure to arsenic and cadmium and the risk of congenital heart defects in offspring. Reproductive Toxicology. 2016; 59: 109–116.