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Original Research Article

Fetal distress and the levels of malondialdehyde (MDA): A meta-analysis

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Abstract

Purpose: *To estimate the effect of malondialdehyde (MDA) level on fetal distress.*
Methods: *Meta-analyses of randomized controlled interventions were performed by searching 8 electronic databases (CNKI, VIP, CBM, WANFANG, Embase, PubMed, Cochrane, and Web of Science) from 1980 – to date for randomized controlled trials to determine any intrapartum fetal distress. A meta-analysis within a frequentist framework was performed and the quality and inconsistency of the trials were assessed. Dual selection and data abstraction were conducted. The methodological quality of the meta-analyses was assessed using AMSTAR, and the quality of evidence was assessed using GRADE. Random-effect models were used to pool results from individual studies included in each meta-analysis.*
Results: *A total of 1720 patients received MDA tests, and the results showed that MDA value of experimental group was 1.66 higher than that of control group. Heterogeneity between the two groups was high, suggesting that the choice of blood source significantly affected the result of meta-analysis ($p < 0.05$). The group of blood samples collected from mothers was highly heterogeneous, and combined with the results of 16 groups, the effective amount reached (2.08) was significant ($z = 4.29$, $p < 0.05$). This means that MDA increase in maternal blood during maternal-fetal distress. Secondly, cord blood samples were highly heterogeneous in the collection group, and the random effect was insignificant ($z = 0.94$, $p > 0.05$).*
Conclusion: *Malondialdehyde level in maternal and cord blood reflects the relationship between fetal distress and adverse outcomes. Further research is needed to confirm the extent to which they are related.*

Keywords: *Malondialdehyde (MDA) level, Fetal distress, Meta-analysis*

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INTRODUCTION

For newborn babies, hypoxia is one of the important factors that can lead to disability and death [1,2]. Fetal distress is a common syndrome in perinatal fetuses, resulting in acidosis and hypoxia [3-5]. Some studies have shown that when the fetus has intrauterine distress or hypoxia, the content of free radicals in the maternal body would show an increasing trend, which may cause damage to the fetus's nervous system. With the increase in fetal hypoxia, the impact of hypoxia on the fetus becomes more serious, eventually causing brain damage [6,7]. This study focused on newborns and analyzed

the correlation between MDA levels, fetal distress, and its adverse outcomes.

METHODS

A systematic review by the researchers was conducted and the result was reported according to established guidelines. A total of 8 electronic databases were searched (CNKI, VIP, CBM, WANFANG, Embase, PubMed, Cochrane, and Web of Science) to assess any randomized control trials on monitoring methods for predicting adverse outcomes of fetal distress via evaluation of MDA levels. The related medical topic headings (MeSH) were consulted and key search terms in the advanced search platform of NICE healthcare database and Google Scholar were used. A supplementary search was performed to identify any missing evidence. No search filters or language restrictions were used. If deemed relevant, articles in non-English languages are obtained and translated. Potentially relevant studies were manually screened in the electronic database and a systematic review of the subject was published to identify any other relevant trials.

The diagnostic criteria for fetal distress was referred to in the sixth edition of Obstetrics and Gynecology [8], which were fetal heart rate, determined as abnormal when it exceeded 160 beats/min or was less than 120 beats/min. Fetal electronic monitoring uterine contraction stress test indicated multiple late decelerations, severe variant deceleration, and other abnormalities. Amniotic fluid II° ~ III° meconium contamination, and abnormal fetal movement - the initial stage is frequent fetal movement, and the fetal movement gradually decreases or decreases in frequency. Fetal scalp blood gas pH value < 7.20, PO_2 < 10 mmHg, and PCO_2 > 60 mmHg [9]. The screening flow chart is shown in Figure 1.

Quality assessment

Two reviewers independently assessed the quality of included studies using the Cochrane risk of bias assessment tool. Each study was assessed for the quality of randomization and sequence generation, assignment concealment, outcome assessment, completeness of outcome data, and selective outcome reporting [10]. Blinding was deemed non-feasible because of the nature of evaluated interventions and was excluded from the quality assessment. Efforts to standardize the management of patients with suspected fetal distress were taken into account when evaluating detection and outcome assessment bias.

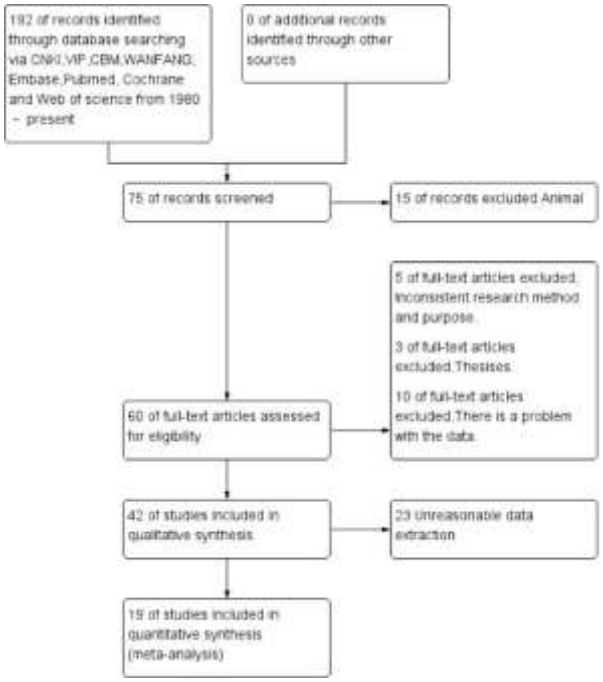

Figure 1: Flow chart of the study

Statistical analysis

A design-by-treatment interaction model was used to check the assumption of consistency in the entire network, assuming a common estimate for the heterogeneity variance across the different comparisons in the network.

The direct and indirect evidences were investigated and inconsistencies were determined by comparing within network using node-splitting approach, assuming (a common heterogeneity estimate within each loop) [11]. A potential source of inconsistency was investigated within relevant trials also. In cases where inconsistency was detected, a network meta-regression related to reference treatment was conducted, testing for 2 potential effect modifiers, gestational age and pregnancy risk status. All analyses were conducted using Stata15.

RESULTS

Heterogeneity test

A total of 19 studies were tested for heterogeneity (I^2 = 98 % > 50 %), and the Q test was p < 0.1, indicating that there was strong heterogeneity among the studies selected. The random effects were selected to perform a meta-analysis, and were also used to investigate the reasons for heterogeneity. Based on the data of this study, it is highly suspected that the source of heterogeneity is that the two groups of blood

samples were different. Subgroup analysis was then carried out according to the classification of the scale in the follow-up. For the 19 articles, random effects were selected for meta-analysis, and the results are shown in Figure 2.

The results of studies for meta-analysis performed by random effects showed that MDA value of experimental group was 1.66 higher than that of control group, and the degree of increase was statistically significant ($p < 0.05$).

Sensitivity analysis

The sensitivity analysis results of the 19 studies are shown in Figure 3.

As shown in Figure 3, based on different pain scales, the study showed different sensitivities. Therefore, it was suspected that the different sources of blood samples caused the heterogeneity. Meta-regression was used to investigate whether the difference in the scale had a significant impact on the effect size.

Meta-regression for heterogeneity

Based on the suspicion that heterogeneity was caused by the different sources of blood samples, the effect size was used as the dependent variable, the blood sample source was grouped as the independent variable, and meta-regression was performed.

Subgroup analysis

According to different sources of blood samples, 19 studies were divided into two groups for subgroup meta-analysis. The results as shown in Figure 4 and Figure 5.

Based on the subgroup analysis above, the heterogeneity between the two groups was very strong, which means that the choice of blood source affected the results of meta-analysis to a great extent. The group of blood samples collected in the mother's body was highly heterogeneous, and combined with results of 16 groups, the random effect amount reached 2.08 and was significant ($z = 4.29$, $p < 0.05$). Hence MDA increased in the maternal blood during maternal-fetal distress. Secondly, cord blood samples were highly heterogeneous in collection group, and combined with results from three kinds of literature, the random effect amount reached -0.50 and was not significant ($z = 0.94$, $p > 0.05$). Therefore, there was no significant difference between the experimental group and the control group.

Bias test

The bias test was conducted according to the subgroups, and the funnel diagram was drawn. The results as shown in Figure 6 A and B.

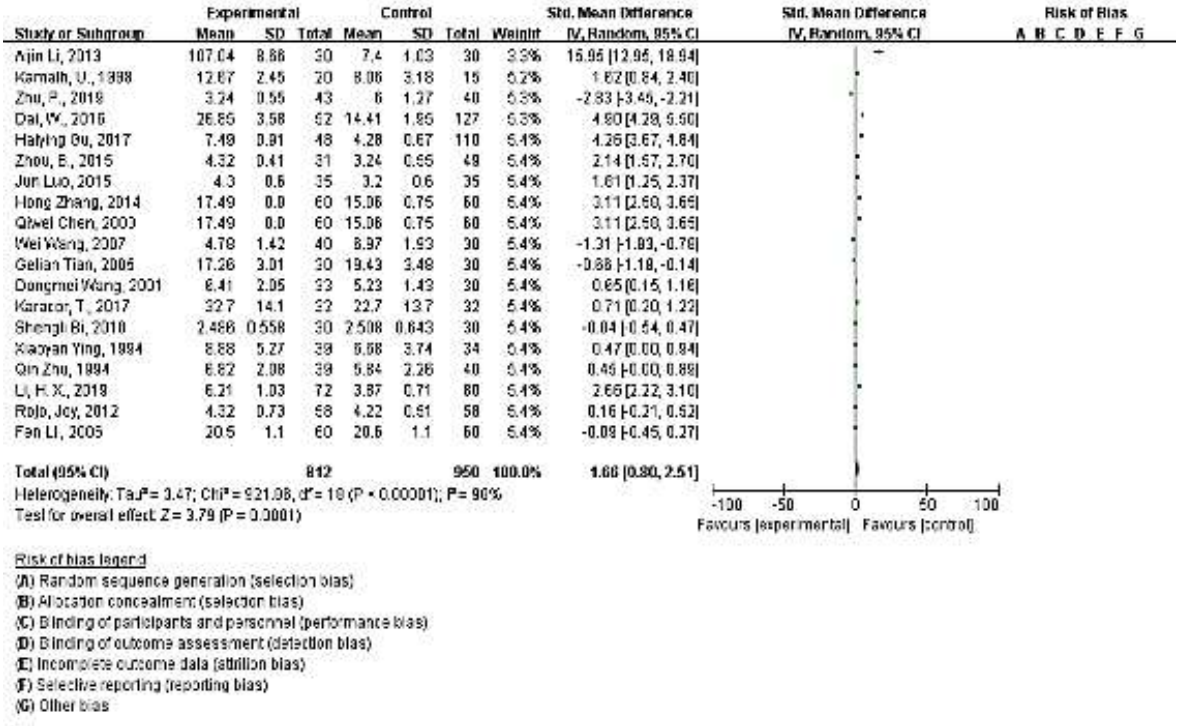

Figure 2: Forest plot of the 19 studies

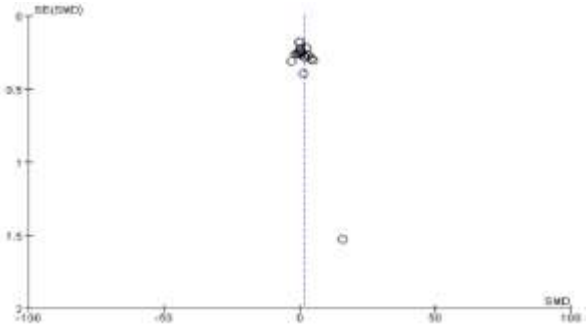

Figure 3: Funnel plot of all the 19 studies

It can be seen from figure 6 that the funnel diagram of this study is symmetrical, and the bias test shows that all $p > 0.05$. It can be assumed that there is no publication bias in the literature of this study.

DISCUSSION

Oxygen free radicals naturally exist in the human body with small content and it is considered maintained in a dynamic equilibrium state. When the body is in a special situation, the oxygen-free radical content in the human body will show a sharp increase and even higher than that of the human body and will further trigger the oxidative stress response.

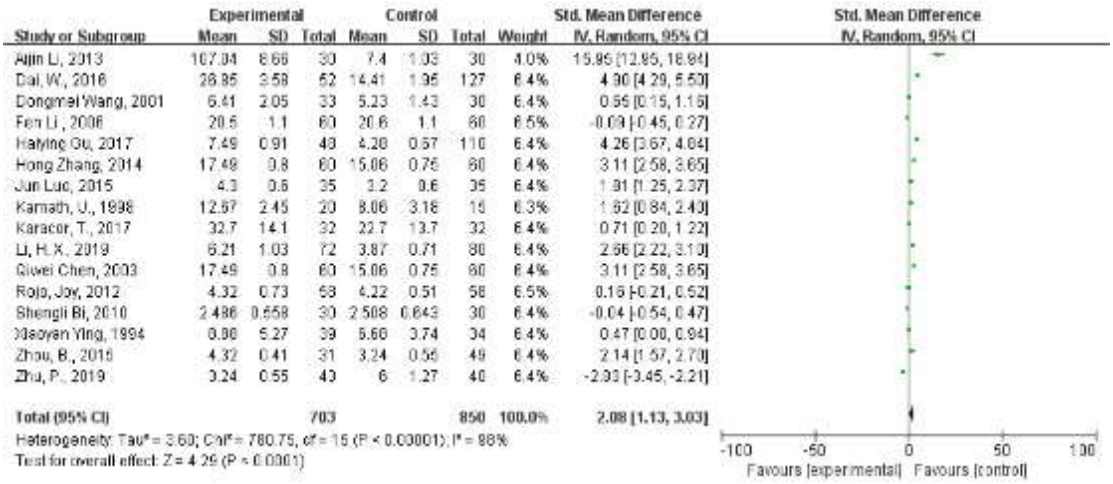

Figure 4: Forest plot of subgroup M

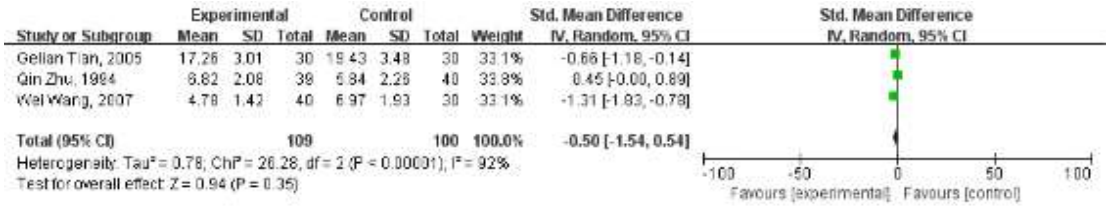

Figure 5: Forest plot of subgroup U

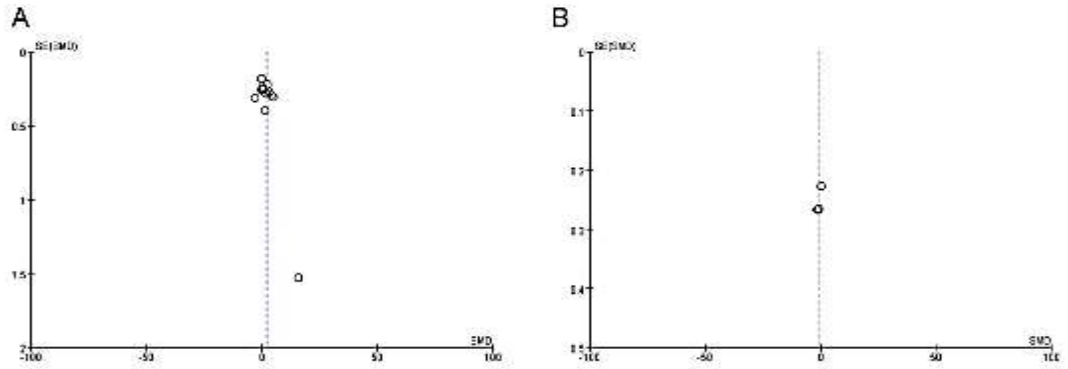

Figure 6: (A) Funnel plot of subgroup M; (B) Funnel plot of subgroup U. Note: M on the left; U on the right; *M=blood sample from mother; *U=blood sample from umbilical cord blood

Long-term clinical studies have confirmed that fetuses in a hypoxic-ischemic state are very likely to suffer from intrauterine distress [12]. In the fetus's oxidative respiratory chain, electron transfer under normal conditions will be hindered, and the fetus oxygen free radical content will increase and cause oxidative stress damage [13].

The fetus's central nervous system is rich in protein and unsaturated fatty acids. Under the influence of oxygen free radicals, the protein and fatty acids in the fetal body will further form an oxidation reaction, which will eventually form a non-biological function, and even will damage the structural substances of fetal cells, where MDA is a substance formed by a series of peroxidation reactions of fats in the fetus. The more severely the fetal cell structure is damaged, the higher the MDA level [14].

Oxidation and antioxidant cause changes in people with fetal distress and normal pregnancy. Oxidation is key to metabolism, mitochondrial respiration, and oxidative phosphorylation, produces ATP and free radicals, and causes cell damage and disease. Under normal circumstances, free radicals are continuously generated during body metabolism but do not cause cell damage [15,16]. The oxidation and antioxidant systems in the body are out of balance, thus producing a large number of free radicals, which exceed the body's ability to remove them, thereby affecting the metabolism of lipids, proteins, sugars, and nucleic acids. Fetal distress is the main cause of perinatal death. It can also lead to neonatal asphyxia and hypoxia, resulting in permanent neurological sequelae.

There are many reasons for fetal distress, and they are related to the mother, umbilical cord, placenta, fetus, and the application of certain drugs, anesthetics, and other factors. Its pathogenesis is very complicated [17]. Studies have reported that for whatever reason, the initiation and production of free radicals were acute [18].

CONCLUSION

The level of MDA in maternal blood reflects the relationship between fetal distress and adverse outcomes to a certain extent, but the level of MDA in cord blood reflects the degree of fetal distress. Due to bias of the included studies and experimental results, the correlation between fetal distress and adverse outcomes cannot be fully proven, and further research is needed to confirm this.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. Yongli Liu and Xiuping Chi contributed equally.

REFERENCES

1. *Aijin L. Effects of compound danshen injection on oxidative stress and pregnancy outcome of oligohydramnios fetus. Chin J Physicians 2013; 15(9): 1250-1252.*
2. *Adeleke BS, Babalola OO. The plant endosphere-hidden treasures: a review of fungal endophytes. Biotechnol Genet Eng 2021; 37(2): 154-177.*

3. Gelian T, Su'an Y, Qingxiong P, Lifang Z. Further study on prevention and treatment of fetal distress with vit-E. Chin J Modern Med 2005; 15(1): 144-147.
4. Vadaye KE, Fazly BB, Kerachian MA. Implantation of stem cells on synthetic or biological scaffolds: an overview of bone regeneration. Biotechnol Genet Eng 2021; 37(2): 238-268.
5. Haiying G, Pengyun L, Yingxue L. Correlation between ultrasound parameters of umbilical cord blood flow in fetal distress and the degree of fetal ischemia-hypoxia injury. J Hainan Med Col 2017; 23(16): 2233-2239.
6. Jun L. Relationship between changes of redox system and fetal distress in patients with intrahepatic cholestasis of pregnancy. Chin J Reproduct Health 2015; (2): 154-156.
7. Qiwei C, Guobin H, Cuilan W, Yuxuan S. Effects of low molecular antioxidants on fetal distress. Chin J Pract Gynecol Obstet 2003; 19(6): 371-372.
8. Bolisetty S, Naidoo D, Lui K, Koh TH, Watson D, Whitehall J. Antenatal supplementation of antioxidant vitamins to reduce the oxidative stress at delivery--a pilot study. Early Hum Dev 2002; 67(1-2): 47-53.
9. Bullens LM, Hulsenboom A, Moors S, Joshi R, van Runnard HP, van der Hout-van DJM, van den Heuvel ER, Guid OS. Intrauterine resuscitation during the second stage of term labour by maternal hyperoxygenation versus conventional care: study protocol for a randomised controlled trial (INTEREST O2). Trials 2018; 19(1): 195.
10. Chelchowska M, Laskowska-Klita T, Leibschang J. The effect of tobacco smoking during pregnancy on concentration of malondialdehyde in blood of mothers and in umbilical cord blood. Ginekol Pol 2005; 76(12): 960-965.
11. Coutinho FG, Diniz EMA, Kandler I, Cianciarullo MA, Santos NRD. Assessment of oxidative damage and enzymatic antioxidant system activity on the umbilical cord blood and saliva from preterm newborns with risk factors for early-onset neonatal sepsis. Rev Assoc Med Bras 2018; 64(10): 888-8895.
12. Tao C, Hu J, Zhang S, Bai X, Zhao C, Zuo Z, et al. Effect of tenofovir disoproxil and telbivudine on the growth and development of infants by blocking mother-to-child transmission of hepatitis B virus. Trop J Pharm Res 2022; 21(9): 1985-1991 doi: 10.4314/tjpr.v21i9.24
13. Qin LN, Feng AH, Yang CH, Xing HY. Clinical values of superoxide dismutase and malondialdehyde detection in cord blood of newborns with fetal distress. Zhonghua fu chan ke za zhi 2005; 40(5): 312-314.
14. Dai W, Xu Y, Ma XW, Zhang L, Zhu MJ. Ultrasonic characteristics and clinical significance of umbilical cord blood flow in acute fetal distress. J Acute Dis 2016; 5(6): 483-487.
15. Kamath U, Rao G, Raghothama C, Rai L, Rao P. Erythrocyte indicators of oxidative stress in gestational diabetes. Acta Paediatr 1998; 87(6): 676-679.
16. Li RL, Yang PY, Chen XY, Wang L. Maternal serum AGEs levels in pregnancies associated with neural tube defects. Int J Dev Neurosci 2014; 33: 57-61.
17. Wang CC, Rogers MS. Lipid peroxidation in cord blood: a randomised sequential pairs study of prophylactic saline amnioinfusion for intrapartum oligohydramnios. Brit J Obst Gynaecol 1997; 104(10): 1145-1151.
18. Karacor T, Sak S, Basaranoglu S, Peker N, Agacayak E, Sak ME, Turgut A, Evsen MS, Evliyaoglu O, Gul T. Assessment of oxidative stress markers in cord blood of newborns to patients with oxytocin-induced labor. J Obstet Gynaecol Res 2017; 43(5): 860-865.