



# **Metabolic Changes in Newborns and Women Who Consumed Small Doses of Alcohol in the Prenatal Period**

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## **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## **ABSTRACT**

**Introduction:** Ethyl alcohol and its metabolites even in low concentrations negatively affects an embryo and a fetus. Interest to the role of the lipid peroxidation-antioxidant defense (LPO-AOD) system has significantly increased in recent years, because this system imbalance leads to the development of oxidative stress (OS), which is accompanied by body's resistance decrease to the adverse environmental and internal factors negative influence, which is one of the most important triggers of so-called free radical pathology.

**Aim:** The aim of research was to determine the concentration and activity of the metabolic system components "lipid peroxidation-antioxidant defense" (LPO-AOD) and the glutathione system components in pregnant women who consumed no more than 2 doses of low-strength alcoholic beverages (beer, champagne, wine) during the first half of pregnancy and their newborns.

**Methods:** The design of the study was prospective and controlled randomized. The study involved 170 pregnant women who were observed in the regional perinatal center of Irkutsk. Two women refused to participate in the study. The main group consisted of 93 women who drank low alcohol beverages (beer, champagne and wine) in the first half of pregnancy (for a period of 7-20 weeks of

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pregnancy). The control group composed of 75 women who did not drink alcohol throughout their pregnancy. In both groups of women for a period of 30-32 weeks of pregnancy, the parameters of the LPO-AOD and glutathione systems had been determined. Similarly, cord blood had been sampled in 66 control group newborns and 53 newborns whose mothers drank alcohol in the first half of pregnancy (main group). Statistical processing of the research results was performed. Statistical processing of the results obtained had been carried out using the software package STATISTICA 10 Stat Soft Inc, USA (license holder - Scientific Centre for Family Health and Human Reproduction Problems) using the T - student and Mann-Whitney test methods.

**Results:** The study revealed the influence of the use of low alcohol beverages (beer, champagne and wine) in an amount of no more than 2 doses on the state of the LPO-AOD and glutathione systems in the blood serum and red blood cells of pregnant women and their newborns. It was found that even a single intake of low alcohol beverages is accompanied by oxidative stress development in women and their newborns. The state of the glutathione system in pregnant women is characterized by a decrease in the content of reduced glutathione (GSH) and glutathione reductase (GR) activity with an increase in the oxidized glutathione (GSSG) and glutathione-S-transferase (GST) levels. In newborns, a decrease in GSH is associated with a decrease in the of GR, GST, and glutathione peroxidase (GPO) activity.

**Conclusion:** Analyzing the data, in distant perspective the negative role of even small doses of low alcohol (beer, champagne and wine) on pregnant women and their newborns metabolism was established.

*Keywords: Metabolism; status of LPO-AOD; glutathione; pregnant women; newborns; alcohol.*

## 1. INTRODUCTION

The damage caused by alcohol goes far beyond the physical and psychological health of a person who drinks alcohol (World Health Organization. Global status report on alcohol and health 2018. Geneva: World Health Organization, 2018). The period of organogenesis in embryonic development is critical in long-term effects of intoxication [1-4]. During these periods, the effect of ethyl alcohol and its metabolites can lead to long-term structural and metabolic changes in the body [5,6]. Acetaldehyde, main product of ethanol metabolism, can form protein complexes, which leads to the activation of enzymes, a decrease in DNA repair, antibody production, depletion of glutathione, impaired oxygen utilization, and increased synthesis of collagen [7,8,9]. These changes in general are expressed in the retardation of fetal growth and fetal development, the occurrence of congenital malformations, lifelong mental and physical disorders, fetal alcohol syndrome (FAS) [1,10,11,12].

It is noted that ethyl alcohol and its metabolites even in low concentrations negatively affect the embryo and the fetus [13]. Provided the direct chemical ethanol influence on the fetus, fetal alcohol syndrome may occur [14,15]. At the same time, the initial state of a mother's metabolic systems is often more simply

considered as an indifferent background against which various abnormalities are formed and which a priori changes little with the alcohol small amount consumption [1,13,11]. At the same time, based on the concept of the active role of the mother's metabolism in the development of the fetus, it can be assumed that even alcohol small amount consumption by a woman during pregnancy will leave a permanent changes in the nonspecific biochemical processes, which through the placental blood flow can express an altering effect on the key structures of the future child baby [16,17].

In the last decade, the attention of not only specialists in the field of basic medicine, but also practitioners has been focused on the study of the role of the LPO-AOD system [18,19], which is closely connected with the violation of the redox status of the whole organism. But at the same time this system also generating numerous biologically active compounds that play an essential role in metabolism [2-4,20].

In order to analyze redox processes, including LPO-AOD, and the state of a number of metabolic reactions associated with them, it is very important to study the glutathione system, which includes determining the concentration of tripeptide forms and enzyme activity [21].

Based on the above, the aim of our research was to determine the concentration and activity of the LPO-AOP and glutathione metabolic systems components in pregnant women who consumed no more than 2 doses of low alcoholic beverages (beer, champagne, wine) during first half of pregnancy and their newborns.

## 2. MATERIALS AND METHODS

The materials and methods should be structured to consist of the following subheadings; site of the study, Study population, Inclusion & Exclusion criteria, procedure, statistical analysis.

### 2.1 Site of the Study and Study Population

This research was conducted based on the regional perinatal center of the city of Irkutsk. The study involved 170 middle-aged pregnant women ( $28.3 \pm 0.7$  years old). Two women refused to participate in the study. To assess the quality and quantity of alcohol beverages with their informed consent, an anonymous survey of 93 women had been conducted (the main group).

### 2.2 Procedure of Enrollment and Allotment

Two face-to-face structured interviews utilized measures developed by the Prevent FAS Research Group [5]. Participants were asked to provide detailed reports about their alcohol consumption during 40 weeks of pregnancy. Following guidance from Sobell & Sobell, [22] Alvik [23], participants were provided with a calendar and asked to memorize personal events, such as holidays and birthdays, that might be associated with alcohol use [24]. The concept of "one drink" as a unit of consumption was not familiar for women in Siberia. Therefore, similar to beverage- and container-specific approaches that have been used in Russia [5] and other countries [25], a beverage-specific approach was utilized to determine standardized alcohol content and volume of alcohol consumption. Participants were provided with a card that showed pictures of alcoholic beverages and containers that are common in Russia, and were asked about the type of beverage, type of container, and number of containers consumed during each month of pregnancy. This information was transformed into ethanol volume. For reporting clarity, drink in milliliters were then

transformed to U.S. standard drink units (i.e., 14 grams of pure alcohol) [5].

The questionnaire has shown that the average alcohol consumption level in the first half of pregnancy (for a period from 7 to 20 weeks) did not exceed two doses, twice as a rule, in form of beer, wine and champagne. The control group composed of 75 women who did not drink alcohol throughout their pregnancy. The pregnant women in the control and main groups were not different in the composition and frequency of somatic pathology, nor were statistically significant differences in smoking revealed.

### 2.3 Inclusion and Exclusion Criteria

The criteria for inclusion of women in the main group were: drinking alcohol during pregnancy; lack of severe somatic pathology; women's affiliation to the European race. The criteria for inclusion women in the control group were: drinking no alcohol during pregnancy; lack of severe somatic pathology; women's affiliation to the European race. Criteria for the exclusion of women from the research: chronic alcohol intoxication; fortified alcohol (vodka, cognac, whiskey, etc.) consumption during pregnancy; concomitant severe somatic pathology; exacerbations of infectious diseases (bacterial and viral); sexually transmitted infections, HIV infection; drug consumption; women's refusal to further maintenance; change of the women's and their children's' residence.

### 2.4 Laboratory Procedure

In the second half of pregnancy (30-32 weeks), fasting blood was taken from women of both groups, plasma and erythrocytes were separated. The parameters of the LPO-AOD and glutathione systems were determined by technology used at the Scientific Centre for Family Health and Human Reproduction Problems [2-4]. The diene conjugates (DCs) and thiobarbituric acid active reacting products (TBA-AP) content were determined as LPO intermediates. The level of total antioxidant activity (AOA), the content of retinol,  $\alpha$ -tocopherol and the activity of superoxide dismutase (SOD) were determined as the components of AOD. The state of the glutathione system was characterized by the concentration of reduced glutathione (GSH), oxidized glutathione (GSSG) and the activity of glutathione reductase (GR), glutathione-S-

transferase (GST) and glutathione peroxidase (GPO).

## 2.5 Statistical Analysis

Statistical processing of the results obtained had been carried out using the software package STATISTICA 10 StatSoftInc, USA (license holder - Scientific Centre for Family Health and Human Reproduction Problems) using the T - student and Mann-Whitney test methods. The difference in the average compared groups was considered statistically significant at  $p < 0.05$ .

## 3. RESULTS

The average body weight of pregnant women at the time of taking the blood was  $68.22 \pm 1.21$  and  $69.13 \pm 0.32$ ; the average height was  $166.3 \pm 0.71$  and  $166.1 \pm 0.30$ .

It was found that women who drank a small amount of low alcohol beverages during pregnancy only once (beer, champagne, wine), compared to pregnant women who did not drink alcohol during pregnancy, there is an imbalance in the LPO-AOD characterized by the activation of the LPO subsystem with an increase in the content of active products that react with thiobarbituric acid. So, the women of the main group have statistically significant increase in the TBA-AP concentration by 42.6%, compared to the same indicator in the control, which indicates a significant contribution of highly reactive carbonyl products of lipid peroxidation to endogenous intoxication syndrome. An increase of the level of TBA-AP occurs on the background of a decrease in total antioxidant activity (AOA), retinol, and SOD activity, which can be qualified as the development of oxidative stress.

Similarly, cord blood was studied in 66 control group newborns and 53 newborns whose mothers drank alcohol in the first half of pregnancy (main group). The average body weight of the newborns in both groups did not differ:  $3263.5 \pm 643.36$  and  $3132.4 \pm 717.24$ ; the average growth is  $50.9 \pm 2.87$  and  $50.1 \pm 4.28$  consequently.

Analysis of the obtained data glutathione system dysregulation was also noted: the concentration of GSH in erythrocytes decreases, and the content of GSSG increases, which is well within a decrease in GR activity in this situation by 21.3% ( $p < 0.05$ ). Indeed, a decrease in GR

activity in women who consumed alcoholic beverages, indicates inhibition of the enzyme main function - the restoration of GSSG to GSH. It is known that a decrease in the concentration of the tripeptide reduced form adversely affects not only the AOD system, but also many other functions in particular, maintenance of endogenous antioxidants in a reduced state, regulation the nitric oxide cycle, biosynthesis and DNA repair, synthesis of proteins and prostaglandins. GSH is a key factor in the so-called  $\lambda$ -glutamyl cycle of the transport of amino acids into cells, etc. GSH playing significant role in the xenobiotics neutralization, which is likely to increase in women of the main group, as evidenced by the fact that we have discovered a compensatory increase in the activity of GST (Table 1), which is involved in the second phase of detoxification with the consumption of GSH. These data, therefore, can be indirect evidence of an increase in the degree of endogenous intoxication in women who consumed alcohol during pregnancy, a kind of or postponed effects of ethyl alcohol in late gestation.

Analysis of lipid peroxidation in newborns from mothers who drank low alcohol (beer, champagne, wine) during pregnancy, revealed LPO activation, increase in the content of cord blood plasma DC by 20.1% in comparing with this indicator in newborns of the control group (Table 1). As to indicators of the AOD subsystem, it was found that in newborns of the main group there was a decrease in the level of total AOA,  $\alpha$ -tocopherol, and SOD activity relative to the control. So, the combination of changes in these parameters in newborns of the main group meets the criteria for the development of OS.

In newborns of the main group, the state of OS is aggravated by a decrease in the concentration of GSH in red blood cells, which may be associated with the observed decrease in GR activity. Apparently, a significant decrease in the content of reduced glutathione (by 9.7%,  $p < 0.05$ ) in this group is critical, as it is accompanied by a decrease in the activity of not only GR, but also other glutathione-dependent enzymes - GST, and GPO (Table 1). In general, a decrease in the GSH concentration and the activity of enzymes involved in its metabolism in the main group of newborns have a negative effect on LPO-AOD and the implementation of the numerous metabolic functions mentioned above.

**Table 1. The content of the components of LPO-AOD system and the glutathione system in women at 30-32 weeks of pregnancy and in the cord blood of newborns from women who consumed not more than two doses of low alcohol beverages (beer, champagne, wine) during first half of pregnancy, M  $\pm$   $\sigma$**

Indicators	Control (women, n = 93) (blood sampling on 30-32 week of pregnancy)	The main group (women, n = 75) (blood sampling on 30-32 week of pregnancy)	Control (newborns, n = 66) (cord blood)	The main group (newborns, n = 53) (cordblood)
CDs ( $\mu\text{mol/L}$ )	2.18 $\pm$ 0.82	1.90 $\pm$ 0.84*	1.39 $\pm$ 0.40	1.67 $\pm$ 0.69*
TBARs ( $\mu\text{mol/L}$ )	0.94 $\pm$ 0.46	1.34 $\pm$ 0.75*	1.33 $\pm$ 0.34	1.33 $\pm$ 0.36
AOA, conv. Units	11.15 $\pm$ 3.50	9.53 $\pm$ 4.15*	9.36 $\pm$ 2.85	8.34 $\pm$ 2.42*
Retinol ( $\mu\text{mol/L}$ )	0.78 $\pm$ 0.28	0.61 $\pm$ 0.22*	0.41 $\pm$ 0.10	0.43 $\pm$ 0.11
$\alpha$ -tocopherol ( $\mu\text{mol/L}$ )	6.80 $\pm$ 2.28	6.37 $\pm$ 2.58	7.16 $\pm$ 1.82	6.29 $\pm$ 1.53*
SOD (U/mgHb)	1.69 $\pm$ 0.15	1.63 $\pm$ 0.19*	1.74 $\pm$ 0.08	1.64 $\pm$ 0.14*
GSH (mmol/L)	2.13 $\pm$ 0.34	2.00 $\pm$ 0.31*	2.26 $\pm$ 0.40	2.04 $\pm$ 0.28*
GSSG (mmol/L)	1.82 $\pm$ 0.37	1.96 $\pm$ 0.45*	2.00 $\pm$ 0.40	2.02 $\pm$ 0.41
GR ( $\mu\text{mol/min/L}$ )	963.8 $\pm$ 380.1	758.5 $\pm$ 382.8*	870.6 $\pm$ 177.8	675.1 $\pm$ 275.4*
GST ( $\mu\text{mol/min/L}$ )	843.2 $\pm$ 250.8	1230.7 $\pm$ 95.4*	1272.3 $\pm$ 276.5	1116.0 $\pm$ 387.4*
GPO ( $\mu\text{mol/min/L}$ )	282.1 $\pm$ 80.2	267.9 $\pm$ 82.0	283.4 $\pm$ 64.6	246.8 $\pm$ 59.4*

Note: \*  $p < 0.05$  compared with the corresponding control

Thus, when small amounts (not more than 2 doses) of low alcohol beverages (beer, champagne, wine) was consumed by women in the first half of pregnancy, dysregulation of the LPO-AOD processes and the glutathione system was revealed in the second half of gestation such women and their newborns, which can be considered as a negative metabolic phenomenon, potentially affecting the implementation of the development program. This allows us to reiterate that the consumption of even a small amount of alcohol leads to a significant long term disbalance of key metabolic systems, both during pregnancy and in offspring.

#### 4. DISCUSSION

Analyzing the results in this report, we can draw a logical conclusion that the consumption of even a small amount of low alcohol beverages during the first half of pregnancy can cause a whole range of changes in the quality and magnitude of changes in redox indicators and serious metabolic changes.

In general, the essence of these changes can be defined as the moderate oxidative stress development, as evidenced by the high level of TBA-AP and a decrease in antioxidant defense parameters with a very likely violation of the expression of morphogenetic genes. It is possible that further malformations in the development of the child and the occurrence of fetal alcohol syndrome (FAS) can be caused not only by the direct impact of alcohol on the fetus, but through an indirect change in the metabolic and other indicators of the mothers. The weak effect of alcoholsmall doses can cause the so-called "butterfly effect", a term widely used in synergetics and describing the enhancement and modification of the response of any system when exposed to a small force. This term has gained great fame thanks to a short story by a famous science fiction writer Ray Bradbury, "A Sound of Thunder, 1952" (Bradbury R. A Sound of Thunder, 1952). Similar effect, or "toxicants imprinting effect during pregnancy" was described by Kolesnikov S. and coauthors [26,27,28]. They found, thatinjected during pregnancy small doses of different toxicants have postponed effect on rats offspring, which after maturation reacted much more intensively to the injection of same toxicants low doses, than control group.

Alterations in the redox status in the CNS was supported by studies demonstrating ethanol—mediated changes in the production and/or

activity of endogenous antioxidants in various organs, including the cerebellum and placenta. Studies reported that during gestation, any dose of alcohol that is consumed may result in developmental changes. The probability of newborn involvement and the severity of the syndrome depend on the dose of alcohol consumed by the mother, her consumption pattern, maternal and fetal blood alcohol levels and metabolism, maternal health, gestational age during which the fetus is exposed, and genetic susceptibility of the fetus as reported by many studies.

Alcohol affects the fetus directly or indirectly, affecting its growth. It interferes with placental transportation of essential nutrients for fetal development; alcohol also may result in maternal malnutrition. Probably more than one mechanism will explain the harmful effects of alcohol on the fetus. Alcohol easily crosses the blood-brain barrier, which may result in complex effects on brain development. It may cause the death of certain brain cells, or may alter their function.

The literature showed that Ethanol can induce oxidative stress directly by formation of free radicals which react with different cellular compounds, or indirectly by reducing intracellular antioxidant capacity, such as decreased glutathione peroxidase levels. A significant increase in oxidative stress was demonstrated in placental villous tissue following two hours of ethanol perfusion, primarily involving the nitric oxide pathway in the trophoblast and DNA damage in the villous stromal cells as per reported studies. This study found that Alcohol-induced oxidative stress leads to increase lipid peroxidation and damage protein and DNA.

#### 5. CONCLUSION

Analyzing the data, in distant perspectivethe negative role of even small doses of low alcohol(beer, champagneand wine) on pregnant women and their newborns metabolism was established So,to minimize the risk of fetal developmental disorders and, in the future, a child developmental disorders, it is necessary to exclude any alcohol beverages consumption during pregnancy. For the prevention of possible complications, it is necessary to recommend to women an antioxidant diet and specific medications that can help maintain the normal redox status of a woman's body.

Author should work more on the discussion; the significance of the study should be elaborated;

More information is needed to defend the result trend. We need to understand how consumption of alcoholic beverages impaired LPO-antioxidant mechanisms. For example, does consumption of alcohol disrupt absorption of tocopherol and other raw materials which are needed for intrinsic antioxidant production or does alcohol interfere with physiologic mechanisms and biochemical pathways involved in endogenous antioxidant synthesis.

## DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

## CONSENT

As per international standard or university standard, Participants' written consent has been collected and preserved by the author(s).

## ETHICAL APPROVAL

This research was approved by the Local Ethics Committee of Scientific Centre for Family Health and Human Reproduction Problems.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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