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Pregnancy and Alcohol: Parameters of Endogenous Intoxication Depending on Blood Phosphatidylethanol Levels

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ABSTRACT

BACKGROUND: Endotoxicosis is a multifactorial pathophysiological process that can significantly affect the mother–placenta–fetus system during gestation. Alcohol consumption is a potential aggravating factor for maternal health, associated with biochemical disturbances both in the mother and the fetus, and may increase the risk of endotoxicosis.

AIM: The work aimed to assess endogenous intoxication in women at different stages of pregnancy by measuring the concentration of middle molecules in venous blood and its association with serum phosphatidylethanol (PEth) levels.

METHODS: Endogenous intoxication was evaluated by middle molecules levels in pregnant women (n=163). In accordance with PEth 16:0/18:1 concentrations, groups of women were identified according to alcohol consumption levels: group 1 with PEth ⩽8 ng/mL (non-drinkers, control); group 2 with 8–45 ng/mL (drinking less than one dose); group 3 with ⩾45 ng/mL (drinking more than one dose). Measurements were performed at 6–12, 18–22, 28–32, and 38–40 weeks of gestation. Plasma samples were used for analysis. Middle molecules were determined at λ=238, 254, 260, and 280 nm, followed by calculation of distribution coefficients (238/260, 238/280, 280/254).

RESULTS: Compared with controls, significant reductions in middle molecules levels (λ=238 nm) were observed in alcohol-consuming women at 28–32 weeks in both group 2 (p=0.013) and group 3 (p=0.003). Before delivery, middle molecules levels were lower in group 3 compared with controls (p=0.004). A significant decrease in middle molecules levels (λ=280 nm) was detected in group 3 compared with group 2 (p=0.017). In alcohol-consuming women, regardless of PEth 16:0/18:1 levels, significantly lower values of the peptide–nucleotide distribution coefficient 238/260 (p=0.007 and p <0.001 in groups 2 and 3, respectively) and aromaticity coefficient 238/280 (p=0.002 and p <0.001 in groups 2 and 3, respectively) were observed compared with controls at 28–32 weeks. Before delivery, decreases in these coefficients were noted only in group 2 (p=0.006 for 238/260; p=0.015 for 238/280). The 280/254 distribution coefficient was higher in alcohol-consuming women at 28–32 weeks compared with controls (p=0.003 and p=0.014 in groups 2 and 3, respectively).

CONCLUSION: The findings indicate reduced levels of specific fractions of middle-molecular toxins reflecting both anabolic and catabolic pools in alcohol-consuming women, which may be associated with serious metabolic disturbances in the mother–placenta–fetus system. Distribution coefficients proved to be sensitive markers for monitoring endogenous intoxication in pregnant women, suggesting a predominance of catabolic processes with accumulation of catabolic products and a possible increased risk of preterm delivery, regardless of alcohol dose.

Keywords: endogenous intoxication; middle molecules; phosphatidylethanol; pregnancy at different stages.

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Беременность и алкоголь: параметры эндогенной интоксикации в зависимости от уровня фосфатидилэтанола в крови

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АННОТАЦИЯ

Обоснование. Эндотоксикоз — многогранный патофизиологический процесс, способный оказать большое влияние на систему «мать–плацента–плод» во время гестации. Злоупотребление спиртосодержащими продуктами — вероятный отягощающий фактор для здоровья беременных, который может сопровождаться биохимическими нарушениями как у матери, так и у плода, в том числе повышать риск развития эндотоксикоза.

Цель. Оценить эндогенную интоксикацию у женщин в разные сроки беременности по содержанию молекул средней массы в венозной крови и её зависимость от уровня сывороточного фосфатидилэтанола (PEth).

Материалы и методы. Оценивали уровень эндогенной интоксикации по содержанию молекул средней массы у беременных (n=163). В зависимости от концентрации PEth 16:0/18:1 были выделены группы женщин, употребляющих разные дозы алкоголя: 1-я группа — значение PEth ⩽8 нг/мл (непьющие, контроль); 2-я группа — от 8 до 45 (пьющие менее одной дозы); 3-я группа — ⩾45 (пьющие более одной дозы). Показатели 4 раза оценивали на сроках гестации 6–12, 18–22, 28–32, 38–40 недель. В качестве материала для исследования использовали плазму крови. Уровень молекул средней массы определяли при λ=238, 254, 260 и 280 нм с последующим расчётом коэффициентов распределения (238/260, 238/280, 280/254).

Результаты. По сравнению с контролем установлено достоверное снижение уровня молекул средней массы (λ=238 нм) у беременных, употребляющих алкоголь на сроке 28–32 недели как во 2-й (p=0,013), так и в 3-й (p=0,003) группе. Перед родами отмечается более низкий уровень молекул средней массы в 3-й группе по сравнению с контролем (p=0,004). Выявлено достоверное снижение уровня молекул средней массы (λ=280 нм) в 3-й группе беременных по сравнению со 2-й группой (p=0,017). У женщин, употребляющих алкоголь, независимо от уровня PEth 16:0/18:1, достоверно значимо более низкие значения пептидно-нуклеотидного коэффициента распределения 238/260 (p=0,007 и p<0,001 во 2-й и 3-й группах соответственно) и коэффициента ароматичности 238/280 нм (p=0,002 и p<0,001 во 2-й и 3-й группах соответственно) по сравнению с контрольной группой на 28–32-й неделе беременности. Перед родами снижение данных коэффициентов отмечено только во 2-й группе (p=0,006 для 238/260 и p=0,015 для 238/280). В группах пьющих женщин коэффициент распределения 280/254 нм был выше на сроке 28–32 недели по сравнению с контролем (p=0,003 и p=0,014 во 2-й и 3-й группах соответственно).

Заключение. Полученные результаты указывают на снижение содержания отдельных фракций среднемолекулярных токсинов, отображающих как анаболический, так и катаболический пулы, в группе женщин, употребляющих алкоголь, что может быть связано с развитием серьёзных метаболических нарушений в системе «мать–плацента–плод». Коэффициенты распределения оказались чувствительными маркерами для отслеживания уровня эндогенной интоксикации в группах беременных, свидетельствуя о превалировании катаболических процессов с накоплением продуктов катаболизма и возможном риске преждевременных родов при употреблении алкоголя независимо от дозы.

Ключевые слова: эндогенная интоксикация; молекулы средней массы; фосфатидилэтанол; беременность разных сроков.

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妊娠与饮酒：血液中磷脂酰乙醇水平与内源性中毒参数的关系

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摘要

论证。内源性中毒是一种多方面的病理生理过程，在妊娠期间可能对“母体 – 胎盘 – 胎儿”系统产生显著影响。饮酒是危害孕妇健康的潜在加重因素，可能伴随母体和胎儿的生化紊乱，并增加内源性中毒发生的风险。

目的。目的：根据静脉血中中分子物质的含量，评估不同妊娠阶段女性的内源性中毒水平，并探讨其与血清磷脂酰乙醇（phosphatidylethanol, PEth）水平的关系。

材料与方法。通过检测孕妇（*n*=163）静脉血中中分子物质的含量来评估内源性中毒水平。根据PEth 16:0/18:1浓度，将孕妇划分为饮酒剂量不同的三组：第1组为PEth ≤8 ng/mL（不饮酒，对照组），第2组为8 – 45 ng/mL（饮酒量少于1个剂量单位），第3组为≥45 ng/mL（饮酒量多于1个剂量单位）。在妊娠6 – 12、18 – 22、28 – 32和38 – 40周四个阶段，对中分子物质进行了四次评估。研究材料为血浆。在λ=238、254、260和280 nm下测定中分子物质的水平，随后计算分布系数（238/260、238/280、280/254）。

结果。与对照组相比，孕28 – 32周时饮酒孕妇在第2组（*p*=0.013）和第3组（*p*=0.003）均表现为λ=238 nm中分子物质水平显著降低。临产前，第3组中分子物质水平低于对照组（*p*=0.004）。发现第3组孕妇的中分子物质水平（λ=280 nm）较第2组显著降低（*p*=0.017）。在孕28 – 32周时，饮酒孕妇无论PEth 16:0/18:1水平高低，其肽 – 核苷酸分布系数238/260（第2组*p*=0.007，第3组*p*<0.001）和芳香性分布系数238/280（第2组*p*=0.002，第3组*p*<0.001）均较对照组显著降低。临产前，仅在第2组观察到这些系数的下降（238/260的*p*=0.006，238/280的*p*=0.015）。在饮酒组中，孕28 – 32周时280/254分布系数高于对照组（第2组*p*=0.003；第3组*p*=0.014）。

结论。结果显示，饮酒孕妇中分子毒素的某些分馏成分反映合成代谢与分解代谢库，其含量降低，这可能与“母体 – 胎盘 – 胎儿”系统发生严重代谢紊乱有关。分布系数对内源性中毒水平的监测较为敏感，表明分解代谢过程占主导并导致分解产物积累，而饮酒无论剂量大小均可能增加早产风险。

关键词：内源性中毒；中分子物质；磷脂酰乙醇；不同孕期。

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BACKGROUND

The development of normal pregnancy is accompanied by a series of adaptive responses aimed at maintaining dynamic homeostasis at all levels to ensure healthy fetal growth [1]. Functional changes in free radical homeostasis and neuroendocrine regulation play a significant role in this process, which may lead to alterations in middle molecule (MM) levels, serving as markers of endogenous intoxication [2]. MMs are biologically active peptide substances, including polyhydric alcohols, aminoglycans, and non-regulatory oligopeptides, depending on the type of diseases and complications; their concentrations increase with enhanced protein catabolism [3–5]. MMs are involved in microcirculatory disturbances, carbohydrate and energy metabolic disorders, and they also inhibit mitochondrial respiration and DNA synthesis. By exacerbating processes, they act as secondary toxins and can be considered prognostic factors of metabolic disorders [6]. MMs have diverse origins: alimentary (from food), from intestinal microbiota metabolites, and endogenous (protein proteolysis products). Due to their varied biological activities—disruption of biomembrane ion permeability, inhibition of enzymatic systems, and binding of essential proteins—they contribute significantly to endotoxicosis [7, 8].

Endotoxicosis is a complex and multifaceted pathophysiological process that profoundly affects the mother–placenta–fetus system during gestation. Pregnancy induces hemodynamic adaptations and alters the lipid profile with the predominance of unsaturated fatty acids and cholesterol, potentially aggravating endogenous intoxication. One of the key pathophysiological mechanisms underlying endotoxicosis is the activation of lipid peroxidation processes triggered by oxygen radicals, along with increased phospholipase system activity. Progression of endotoxicosis in pregnant women is further promoted by hormonal imbalance, diabetes mellitus, liver diseases, and impaired detoxification systems [9, 10]. These disturbances may occur in the context of maternal alcohol consumption. Ethanol, even at low doses, exerts detrimental effects on the embryo. Several fetal neurophysiological pathologies induced by ethanol are now collectively recognized as fetal alcohol syndrome, observed in approximately half of children born to women with alcohol dependence. During pregnancy, ethanol exposure may lead to oligohydramnios, placental aging, severe toxicosis, and accumulation of toxic metabolites in the amniotic fluid [11]. It has been shown that levels of lipid peroxidation intermediates are significantly higher in alcohol-consuming women compared with controls [12].

It is believed that MMs can penetrate the placental barrier and exert adverse effects on the fetus, causing various multiorgan disturbances [13]. The risk of impaired development of the fetus and placenta increases during critical periods of pregnancy because of hormonal insufficiency (6–12 weeks), the development of isthmic–cervical insufficiency, as well as gestational diabetes mellitus and pre-eclampsia (18–22 weeks), late gestosis, placental insufficiency, and premature placental abruption (28–32 weeks). Therefore, it is of particular interest to assess the levels of these factors at these specific time points. In addition, from week 38, the maternal organism undergoes intensive preparation for the upcoming delivery; this period is extremely important because fetal development is fully completed [14].

Known alcohol biomarkers are considerably variable in sensitivity and specificity [15]. The most reliable marker for the detection of ethanol intoxication is phosphatidylethanol (PEth), the determination of which in biological fluids is considered a promising method for diagnosing episodic alcohol intake and chronic alcohol intoxication. PEth is a glycerophospholipid formed from phosphatidylcholine in various tissues in the presence of ethanol. Because of its long half-life after alcohol consumption, PEth accumulates in the blood and can be detected for up to 28 days after alcohol intake [16, 17]. To date, 48 PEth homologues have been identified, among which PEth 16:0/18:1 is the most informative [18].

The study aimed to assess endogenous intoxication by the concentration of MMs in venous blood of women depending on serum phosphatidylethanol levels at different stages of pregnancy.

MATERIALS AND METHODS

The study was conducted from 2021 to 2024 in accordance with the Declaration of Helsinki of the World Medical Association (1964, amended 2013) and was approved by the Biomedical Ethics Committee of the Scientific Center for Family Health and Human Reproduction (meeting extract No. 2 of March 4, 2021). The written informed consent was obtained from all participants.

A prospective study included 163 pregnant women receiving care at Irkutsk City Clinical Hospital No. 8. The sample size was not pre-determined. Inclusion criteria: current pregnancy; age 18–40 years; signed informed consent; regular follow-up at the medical facility. Non-inclusion criteria: HIV infection; viral hepatitis; diabetes mellitus; exacerbation of chronic diseases; acute respiratory viral infection; COVID-19; participation in an in vitro fertilization program; sexually transmitted infections; arterial hypertension. Exclusion criteria: withdrawal of consent, protocol violations, technical problems with samples, gestational diabetes mellitus, pre-eclampsia, and thyrotoxicosis. The parameters were evaluated according to gestational age at 6–12, 18–22, 28–32, and 38–40 weeks of pregnancy. The exclusion criteria and deliveries before 38 weeks of gestation resulted in a subset of women unable to provide biological samples at all four time points.

The group distribution was as follows:

- 6–12 weeks of gestation: group 1, $n = 62$; group 2, $n = 66$; group 3, $n = 35$;
- 18–22 weeks of gestation: group 1, $n = 53$; group 2, $n = 57$; group 3, $n = 35$;

- 28–32 weeks of gestation: group 1, *n* = 43; group 2, *n* = 49; group 3, *n* = 28;
- 38–40 weeks of gestation: group 1, *n* = 34; group 2, *n* = 35; group 3, *n* = 14.

Based on PEth concentrations, groups of women were identified according to alcohol consumption levels: group 1 with PEth ⩽8 ng/mL (non-drinkers, control); group 2 with 8–45 ng/mL (drinking less than one dose); group 3 with ⩾45 ng/mL (drinking more than one dose) [12].

Fasting blood samples were collected from the median cubital vein according to standard procedures. The quantitative determination of the direct alcohol biomarker PEth 16:0/18:1 in plasma was performed using High-Performance Liquid Chromatography–Mass Spectrometry on Shimadzu LCMS-8060 system (Japan). The validated lower limit of quantification for PEth 16:0/18:1 was 1 ng/mL.

MM levels were measured at four wavelengths (238, 254, 260, and 280 nm) using SF-2000 spectrophotometer (Russia) [19]. MM fractions were expressed in arbitrary units (AU) of optical density. Distribution coefficients (238/260, 238/280, 280/254) were also calculated.

Statistical analysis was performed using STATISTICA 10.0 software (StatSoft Inc, USA). The normality of distribution for continuous variables was assessed with the Lilliefors-corrected Kolmogorov–Smirnov test and the Shapiro–Wilk test. Because the data were normally or near-normally distributed, results were presented as means and standard deviations (m ± SD). Intergroup differences were assessed using the parametric Student *t*-test with Bonferroni correction; differences were considered statistically significant at $p \leqslant 0.017$.

RESULTS

MM levels at different stages of pregnancy in the study groups are shown in Table 1. At 28–32 weeks, a decrease in MM levels (λ = 238 nm) was observed in alcohol-consuming pregnant women compared with controls, regardless of PEth blood levels ($p = 0.013$ and $p = 0.003$ in groups 2 and 3, respectively). Before delivery, MM levels were lower in group 3 compared with controls ($p = 0.004$). A significant decrease in MM levels (λ = 280 nm) was detected in group 3 compared with group 2 ($p = 0.017$).

The calculation of distribution coefficients showed that, compared with controls, alcohol-consuming women, regardless of the PEth 16:0/18:1 concentration, had significantly lower values of the 238/260 distribution coefficient ($p = 0.007$ and $p < 0.001$ in Groups 2 and 3, respectively) and the 238/280 distribution coefficient ($p = 0.002$ and $p < 0.001$ in Groups 2 and 3, respectively) at 28–32 weeks of gestation (Table 2). Before delivery, decreases in these coefficients were noted only in group 2 ($p = 0.006$ for 238/260; $p = 0.015$ for 238/280). The 280/254 distribution coefficient was higher in alcohol-consuming women at 28–32 weeks compared with controls ($p = 0.003$ and $p = 0.014$ in Groups 2 and 3, respectively).

DISCUSSION

The mechanisms of biochemical adaptation in normal pregnancy and in obstetric diseases involve changes in the placental metabolic regulation. The development of pregnancy are characterized by improved oxygen delivery to the fetus and placenta due to thinning of the placental membrane, which facilitates the transfer of MMs across the placental barrier and their effects on the fetus [20, 21].

More intensive catabolic processes in the third trimester of normal pregnancy, compared with alcohol-consuming women, are indicated by higher levels of peptide substances absorbing at 238 nm. The increased production of reactive oxygen species occurs due to the enhanced metabolism, high oxygen consumption, and fatty acid utilization. During the third trimester, insulin resistance increases, fat catabolism and release of free fatty acids intensify, leading to the increased hydrogen peroxide production [22]. The MM238 includes catabolic products, natural degradation products of cells and tissues, and microbial particles [23]. Lower values of these parameters in the third trimester in alcohol-consuming pregnant women may indicate lower catabolic activity and immunogenesis during this period, which, together with reduced anabolic intensity, adversely affects the mother–placenta–fetus system.

It is known that MM280 reflects the anabolic pool and demonstrates activation of reparative and synthetic processes in cells and tissues. At this wavelength, phenols, tyrosine, tryptophan, and phenylalanine—important for neuronal processes—have maximal absorption. Several studies have demonstrated the impaired synthesis and metabolism of aromatic amino acids with alcohol consumption. Altered metabolism of these amino acids leads to central nervous system neurotransmitter imbalance, which underlies psychiatric and neurological disorders in alcoholism [24].

Endogenous intoxication may result both from elevated concentrations of certain substances and from the disruption of equilibrium between components of homeostatic processes. For this reason, calculation of coefficients provides an additional meaningful characteristic of the development and severity of pathologic processes. The peptide-to-nucleotide coefficient at 238/260 nm reflects the ratio of peptide content shifts, whereas the aromaticity coefficient at 238/280 nm reflects the ratio of aromatic to nonaromatic chromophores [25].

A decrease in aromaticity coefficient with alcohol consumption, regardless of dose, beginning at 28 weeks of gestation may indicate increased cellular synthesis of biologically active compounds promoting labor activity and potentially contributing to pre-term birth. A decrease in the peptide-to-nucleotide coefficient in these groups suggests accumulation of toxic metabolic products (incomplete protein breakdown products and hydrophobic toxins), which may result from consumption of ethanol-containing products.

The ratio of the 280/254 fractions in Groups 2 and 3 was higher than in controls. An increase in this parameter

Table 1. Level of middle molecules (MM) at different stages of pregnancy in the studied groups of women (M±SD)

Gestational age	Group 1	Group 2	Group 3	Significance level
		MM238		
6–12 weeks	0.30±0.21	0.27±0.12	0.24±0.16	–
18–22 weeks	0.27±0.14	0.29±0.15	0.29±0.13	–
28–32 weeks	0.34±0.17	0.26±0.13	0.22±0.12	p_{1-2}=0.013 p_{1-3}=0.003
38–40 weeks	0.33±0.16	0.27±0.16	0.19±0.09	p_{1-3}=0.004
		MM254		
6–12 weeks	0.23±0.16	0.19±0.09	0.21±0.12	–
18–22 weeks	0.21±0.09	0.22±0.09	0.22±0.10	–
28–32 weeks	0.23±0.11	0.20±0.07	0.20±0.07	–
38–40 weeks	0.23±0.10	0.21±0.07	0.18±0.04	–
		MM260		
6–12 weeks	0.22±0.10	0.21±0.08	0.22±0.12	–
18–22 weeks	0.25±0.29	0.23±0.09	0.23±0.10	–
28–32 weeks	0.23±0.11	0.22±0.06	0.21±0.07	–
38–40 weeks	0.23±0.11	0.23±0.06	0.19±0.05	–
		MM280		
6–12 weeks	0.28±0.12	0.25±0.08	0.27±0.13	–
18–22 weeks	0.26±0.10	0.29±0.10	0.29±0.10	–
28–32 weeks	0.30±0.13	0.29±0.10	0.28±0.08	–
38–40 weeks	0.31±0.12	0.30±0.07	0.24±0.06	p_{2-3}=0.017

Table 2. Distribution coefficients at different stages of pregnancy in the studied groups of women (M±SD)

Gestational age	Group 1	Group 2	Group 3	Significance level
		238/260		
6–12 weeks	1.38±0.72	1.41±0.90	1.09±0.66	–
18–22 weeks	1.31±0.62	1.27±0.54	1.29±0.54	–
28–32 weeks	1.48±0.62	1.15±0.54	0.99±0.47	p_{1-2}=0.007 p_{1-3} <0.001
38–40 weeks	1.51±0.63	1.13±0.48	1.04±0.57	p_{1-2}=0.006
		238/280		
6–12 weeks	1.11±0.64	1.18±0.98	0.87±0.50	–
18–22 weeks	1.07±0.52	1.02±0.43	1.01±0.39	–
28–32 weeks	1.15±0.47	0.86±0.41	0.76±0.38	p_{1-2}=0.002 p_{1-3} <0.001
38–40 weeks	1.12±0.47	0.86±0.39	0.82±0.44	p_{1-2}=0.015
		280/254		
6–12 weeks	1.33±0.29	1.34±0.27	1.37±0.25	–
18–22 weeks	1.30±0.22	1.38±0.27	1.35±0.23	–
28–32 weeks	1.33±0.21	1.48±0.25	1.47±0.25	p_{1-2}=0.003 p_{1-3}=0.014
38–40 weeks	1.41±0.27	1.45±0.19	1.39±0.16	–

may indicate intensified catabolic processes, more active lipid peroxidation, and enhanced immunogenesis. Previous studies have shown that even minimal alcohol intake in the first trimester of pregnancy activates lipid peroxidation processes [12].

The processes occurring during ethanol metabolism promote oxidation of proteins and lipids, DNA destruction, and mitochondrial dysfunction, all of which ultimately lead to apoptosis and cellular injury. The disruption of key placental functions occurs as a result of destructive and proliferative changes induced by the toxic effects of alcohol. Chronic alcohol intoxication leads to reduced placental mass and dystrophic and necrotic changes in the chorionic epithelium, which may subsequently manifest as chronic fetoplacental insufficiency, fetal hypoxia, and growth restriction [26, 27].

Elevated levels of progesterone, cortisol, prolactin, estradiol, and other hormones are characteristic of the hormonal shift during gestation [28], which, in turn, may intensify free radical oxidation processes [29, 30] and alter the pool of middle-mass peptides. It has been shown that the harmful effects of ethanol involve stimulation of the hypothalamic–pituitary–adrenal system, with the potential for overstrain and failure of compensatory mechanisms, leading to imbalance in redox status [31]. In addition, women with the laboratory-confirmed alcohol consumption in early gestation are significantly more likely to experience intrauterine growth restriction, anemia, and pre-term birth [11], which may be associated with the involvement of imbalance in the prooxidant–antioxidant system and alterations in the pool of middle-molecular peptides.

This study has several limitations. First, not all pregnant women were able to provide biological material for analysis at all gestational time points because of the exclusion criteria. Second, alcohol consumption by each woman at all stages of pregnancy was not assessed, which precluded longitudinal observation of changes in middle-molecular fractions across gestational ages in the same participant. Future studies are planned to define groups of women and investigate changes in MM concentrations longitudinally, depending on alcohol consumption in different trimesters of pregnancy.

CONCLUSION

The findings indicate reduced levels of specific fractions of middle-molecular toxins reflecting both anabolic and catabolic pools in alcohol-consuming women, which may be associated with serious metabolic disturbances in the mother–placenta–fetus system. Distribution coefficients proved to be sensitive markers for monitoring endogenous intoxication in pregnant women, suggesting a predominance of catabolic processes with accumulation of catabolic products and a possible increased risk of pre-term delivery, regardless of alcohol dose.

The problem of alcohol use in the modern stage of social development remains one of the most urgent issues, the resolution of which may reduce the risk of gestational complications and fetal malformations. Monitoring the levels of middle-molecular toxin fractions may help in decision-making regarding pharmacologic correction or educational interventions for pregnant women.

ADDITIONAL INFORMATION

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