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Age-Related Dynamics of Liver Morphometric Changes and Hemostasis Parameters in Rats Following Prenatal Hypoxia

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Abstract. *To study the long-term consequences of severe intermittent prenatal hypoxia on liver structure and hemostatic system dynamics in rats at different postnatal developmental stages. Pregnant Wistar rats were exposed to normobaric hypoxia (5% O_2, 20 min/day) during embryonic, pre-fetal, or fetal gestation periods. Liver morphometric parameters (hepatocyte and nuclear areas, nuclear-cytoplasmic ratio) and hemostatic indicators (fibrinogen, activated partial thromboplastin time [aPTT], and plasma heparin tolerance [PHT]) were evaluated in offspring at 1, 3, and 6 months of age. At 1 month, hypoxia-exposed animals showed a 19–25% liver mass decrease versus controls ($p < 0.001$), hydropic hepatocyte degeneration, increased cell size, and systemic hypocoagulation. By 3 and 6 months, hepatocyte and nuclear sizes normalized. However, relative liver mass remained elevated ($p < 0.01$), with histology revealing persistent sinusoidal congestion and venous stasis. Concurrently, an age-related inversion from hypocoagulation to a procoagulant state occurred. In 6-month-old rats, fibrinogen increased, aPTT shortened, and PHT decreased to 56–77% of control values ($p < 0.01$). Severe prenatal hypoxia induces a biphasic adaptive response. Despite* morphometric parenchymal recovery, hepatic vascular remodeling and microcirculatory disorders *persist into adulthood, likely driving the development of a long-term procoagulant phenotype.*

Keywords: *blood coagulation, fetal programming, hepatocytes, microcirculation, venous stasis*

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Prenatal hipoksiya təsirinə məruz qalmış siçovullarda qaraciyərin morfometrik göstəricilərinin və hemostaz sistemi parametrlərinin yaş dinamikası

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Xülasə. *Tədqiqatın məqsədi postnatal inkişafın müxtəlif mərhələlərində kəskin prenatal hipoksiyanın siçovullarda qaraciyərin strukturuna və hemostaz sisteminin dinamikasına göstərdiyi uzunmüddətli təsirləri öyrənmək olmuşdur. Boğaz Wistar cinsli siçovullar rüşeym, dölönü və döl inkişaf mərhələlərində normobarik hipoksiyaya (5% O_2, gündə 20 dəqiqə) məruz qoyulmuşdur. 1, 3 və 6*

aylıq yaş dövrlərində qaraciyərin morfometrik göstəriciləri (hepatositlərin və nüvələrin sahəsi, nüvə-sitoplazma nisbəti) və hemostaz parametrləri (fibrinogen, aktiv parsial tromboplastin müddəti və plazmanın heparinə tolerantlığı) qiymətləndirilmişdir. Bir aylıq yaşda prenatal hipoksiyaya məruz qalmış heyvanlarda nəzarət qrupu ilə müqayisədə qaraciyərin kütləsinin 19–25% azalması ($p < 0,001$), hepatositlərdə vakuolizasiya, hüceyrə ölçülərinin artması və sistemik hipokoaqulyasiya müşahidə olunmuşdur. Üç və altı aylıq yaşlarda hepatositlərin və onların nüvələrinin ölçüləri normallaşmışdır. Bununla belə, qaraciyərin nisbi kütləsi yüksək olaraq qalmış ($p < 0,01$), histoloji müayinədə isə sinusoidlərin davamlı dolğunluğu (konqestiyası) və venoz durğunluq aşkar edilmişdir. Eyni zamanda, yaş artdıqca hemostaz sistemində hipokoaqulyasiya vəziyyətindən hiperkoaqulyasiya vəziyyətinə keçid baş vermişdir. Altı aylıq siçovullarda fibrinogenin konsentrasiyası artmış, aktiv parsial tromboplastin müddəti qismən qısalmış, plazmanın heparinə tolerantlığı isə nəzarət göstəricilərinin 56–77%-nə qədər azalmışdır ($p < 0,01$). Beləliklə, kəskin prenatal hipoksiya iki mərhələli adaptiv cavab reaksiyasının formalaşmasına səbəb olur. Qaraciyər parenximasının morfometrik göstəriciləri bərpa olunsa da, qaraciyər damar sisteminin yenidən qurulması və mikrosirkulyasiya pozğunluqları yetkinlik dövrünədək davam edir və ehtimal ki, uzunmüddətli prokoaqulyant fenotipin inkişafının əsas patogenetik mexanizmlərindən biri kimi çıxış edir.

Açar sözlər: *qanın laxtalanması, dölün inkişafı, hepatositlər, mikrosirkulyasiya, venoz durğunluq*

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Introduction

Prenatal hypoxia (PH) remains one of the most frequent causes of intrauterine developmental disorders and adverse perinatal outcomes. Oxygen deficiency during critical periods of ontogenesis can exert a long-term influence on the formation of fetal organs and systems. According to the Developmental Origins of Health and Disease (DOHaD) concept, adverse exposures during early developmental periods can program an increased susceptibility to various diseases in adulthood (Glukman et al., 2016). Experimental studies demonstrate that the consequences of prenatal hypoxia persist far beyond the neonatal period and are associated with an elevated risk of metabolic, cardiovascular, and neuroendocrine disorders (Vetrovoy et al., 2020; Vetrovoy et al., 2021, Smith et al., 2022, Ducsay et al., 2018). Recent studies in large animals also indicate that hypoxic pregnancy is accompanied by the development of fibrotic and metabolic changes in the fetal liver (McGuckin et al., 2025).

The fetal liver—a central metabolic organ that plays a crucial role in metabolism, hematopoiesis, and hemostasis regulation—is one of the primary targets of hypoxic injury. Accumulated data suggest that prenatal hypoxia can disrupt the growth and differentiation of hepatocytes, alter the formation of hepatic tissue, and lead to long-term metabolic consequences (McGuckin et al., 2025, Cao et al., 2019). Furthermore, antenatal hypoxic exposure has been shown to induce structural alterations in the liver, affecting not only the parenchyma but also the stromal-vascular component of the organ (Zotova et al., 2024).

Morphometric research methods are widely used to quantitatively assess the nature and severity of structural changes in the liver. Analysis of hepatocyte dimensions, their nuclear size, and the nuclear-cytoplasmic ratio allows for an objective evaluation of cell damage, compensatory hypertrophy,

polyploidization, and regeneration of liver tissue (Prus et al., 2021, Donne et al., 2021, Matsumoto et al., 2022).

The potential link between structural changes in the liver and disorders of the hemostatic system is of particular interest. Since the liver is the primary site for the synthesis of most clotting factors, fibrinogen, and natural anticoagulants, any changes in its structural and functional state can potentially alter the coagulation profile of the body (Tsaousi et al., 2023). It has previously been shown that prenatal hypoxia can lead to long-lasting alterations in the hemostatic balance of the offspring (Jafarova 2023). Structural damage to the sinusoidal endothelium of the liver, the development of endothelial dysfunction, and microcirculatory disorders are considered among the possible mechanisms underlying these impairments (Gracıa-Sancho et al., 2021).

Despite a substantial body of research dedicated to the consequences of intrauterine hypoxia, most studies focus predominantly on the early postnatal period or isolated aspects of metabolic disorders. Meanwhile, the age-related dynamics of liver structural remodeling after prenatal hypoxia, the specifics of its postnatal recovery, and the potential relationship between morphological changes and hemostatic disorders remain insufficiently understood. In addition, the question of whether the gestational timing of the hypoxic exposure influences the nature and severity of long-term consequences remains unresolved.

In view of this, the objective of the present study was to investigate the age-related dynamics of liver morphometric parameters and hemostatic system indicators in rat offspring following exposure to severe intermittent prenatal hypoxia during different periods of intrauterine development.

Materials and Methods

Animals and Study Design. The study included 120 male Wistar rat offspring, examined at 1, 3, and 6 months of age. All procedures complied with EU Directive 2010/63/EU and were approved by the local Bioethics Committee (Protocol No. 3, April 27, 2021). Animals were housed under standard vivarium conditions (22 ± 2 °C, 50–60% humidity, 12-h light/dark cycle) with ad libitum access to water and pelleted feed. Pregnant females (n = 74) were randomly assigned to a control group (standard conditions) and three experimental groups exposed to prenatal hypoxia during specific gestational windows: embryonic (days 1–7), pre-fetal (days 8–14), and fetal (days 15–21) (Vetrovoy et.al., 2021, Graf et.al., 2022). To minimize litter effects and prevent pseudoreplication, only 1–2 males were randomly selected per litter. Each age and exposure subgroup comprised 10 independent biological replicates.

Modeling of Prenatal Hypoxia. Severe intermittent prenatal hypoxia was induced using a normobaric chamber. Pregnant females were exposed daily to a 5% O_2 / 95% N_2 gas mixture for 20 min during their assigned gestation period (Vetrovoy et al., 2021). Oxygen levels were continuously monitored using a gas analyzer. This established protocol effectively replicates severe hypoxic stress and placental insufficiency (Salyha & Oliynyk, 2023).

Biological Sample Collection. Under intramuscular ketamine anesthesia (0.1 mL/100 g body weight), blood was drawn from the inferior vena cava into 0.1 M sodium oxalate at a 10:1 ratio. The animals were then euthanized via an anesthetic overdose. Livers were rapidly excised, weighed to determine absolute mass, and sampled for histology.

Histological Examination and Liver Morphometry. Liver tissues were fixed in 4% neutral buffered formalin, paraffin-embedded, and sectioned (5 μm) for standard hematoxylin and eosin staining (Korzhevsky & Gilyarov, 2010). Sections were examined using an NU-2 Carl Zeiss microscope (Jena, Germany) equipped with a Motic digital camera. Blinded morphometric analysis was performed using Motic Images Plus 3.0. For each animal, at least 50 intact hepatocytes across five

non-overlapping fields (×500) were analyzed for cell and nuclear diameters and areas. The nuclear-cytoplasmic index (NCI) was calculated. Additionally, binucleated hepatocytes were counted across 50 random fields at ×500 magnification (Prus et al., 2021).

Hemostasis System Assessment. Blood was centrifuged to isolate plasma. Coagulation parameters reflecting the coagulation potential and hepatic protein synthesis—fibrinogen concentration, activated partial thromboplastin time (aPTT), and plasma heparin tolerance (PHT)—were measured using a Coatron M semi-automated coagulometer (TECO Medical Instruments, Germany) and commercial Hemostat kits (Human GmbH, Germany).

Statistical Analysis. Data were analyzed in jamovi (v. 2.6.44) (jamovi project. 2024) and expressed as mean ± standard deviation (M ± SD). Normality and variance homogeneity were verified using the Shapiro-Wilk and Levene's tests, respectively. Age-specific comparisons were conducted using one-way ANOVA with Tukey's post hoc test, or Welch's ANOVA with the Games-Howell post hoc test for heteroscedastic data. Statistical significance was set at $p < 0.05$.

Results

Liver Morphometric Changes

Changes in One-Month-Old Animals. At one month of age, the offspring exposed to prenatal hypoxia exhibited a statistically significant decrease in both absolute and relative liver mass compared to the control group (Table 1). The absolute liver mass was 19–25% lower than the control values ($p < 0.001$), while the relative organ mass decreased by 20–22% ($p < 0.001$). No statistically significant differences were found between the groups exposed to hypoxia at different gestational stages ($p > 0.05$).

Histological examination of the liver in control animals revealed a preserved parenchymal architecture with clearly contoured hepatocytes and centrally located nuclei. In the experimental groups, moderate vacuolization of the hepatocyte cytoplasm was observed, along with an increase in the size of the cells and their nuclei (Fig. 1A). The results of the morphometric analysis corroborated the histological findings. Hepatocyte diameter in the experimental groups exceeded the control values by 16–20% ($p < 0.01$–0.001), and the cell area was larger by 44–49% ($p < 0.05$) (Table 1). Similar changes were recorded for the nuclear apparatus: the nuclear diameter increased by 32–34%, and the nuclear area increased by 75–78% compared to the control.

The nuclear-cytoplasmic ratio was significantly elevated in the pre-fetal period group ($p < 0.05$), while a similar trend was observed in the other experimental groups. Furthermore, an increase in the number of binucleated hepatocytes was noted in the livers of the experimental animals (Fig. 1B). No statistically significant differences were detected among the experimental groups for the majority of the morphometric parameters ($p > 0.05$).

Table 1

Liver morphometric parameters in one-month-old offspring under normal development and after prenatal hypoxia at different stages of embryogenesis

Morphometric indicator	Control (n=10)	Embryonic period (n=10)	Pre-fetal period (n=10)	Fetal period (n=10)
Absolute liver mass, mg	2554.0 ± 53.9	1910.0 ± 12.6 ***	2010.0 ± 5.9 ***	2058.0 ± 54.5 ***
Relative liver weight, %	4.27 ± 0.04	3.32 ± 0.01 ***	3.40 ± 0.07 ***	3.41 ± 0.02 ***
Hepatocyte diameter, µm	16.5 ± 0.9	19.2 ± 1.7 **	19.8 ± 1.9 ***	19.5 ± 1.1 ***

Nuclear diameter, μm	6.67 ± 0.50	8.83 ± 1.52 **	8.91 ± 1.08 ***	8.89 ± 1.54 **
Hepatocyte area, μm²	206.7 ± 27.4	297.0 ± 73.6 *	307.8 ± 90.8 *	298.5 ± 87.4 *
Nuclear area, μm²	34.9 ± 18.4	61.2 ± 5.5 **	61.2 ± 6.0 **	62.3 ± 16.8 *
NCI	0.20 ± 0.04	0.24 ± 0.02	0.26 ± 0.02 *	0.24 ± 0.01

Note. Data are presented as M ± SD. NCI — nuclear-cytoplasmic index. Statistical significance of differences compared to the control group: *p < 0.05, **p < 0.01, ***p < 0.001.

Changes in Three-Month-Old Animals. By three months of age, the absolute liver mass of the animals in the experimental groups did not differ significantly from the control values (p > 0.05) (Table 2). However, the relative liver mass remained significantly higher in the embryonic (p = 0.045) and pre-fetal (p < 0.001) exposure groups. In most cases, the morphometric parameters of hepatocytes and their nuclei did not differ among the groups. The cell diameter and area, as well as the nuclear dimensions, were comparable to the control values (all p > 0.05).

In the pre-fetal exposure group, a significant decrease in the nuclear-cytoplasmic index was noted compared to the control (p = 0.004). In the other groups, the values of this parameter did not differ from those of the control. Despite the absence of pronounced differences in the primary morphometric parameters, histological examination of the livers from the experimental groups revealed sinusoidal dilation and blood stasis in the vascular bed (Fig. 1C).

Table 2

Liver morphometric parameters in three-month-old offspring under normal development and after prenatal hypoxia at different stages of embryogenesis

Morphometric indicator	Control (n=10)	Embryonic period (n=10)	Pre-fetal period (n=10)	Fetal period (n=10)
Absolute liver mass, mg	5600 ± 606.7	5283 ± 418.3	5300 ± 104.9	5237 ± 86.2
Relative liver weight, %	4.06 ± 0.05	4.12 ± 0.03 *	4.23 ± 0.07 ***	4.12 ± 0.04
Hepatocyte diameter, μm	20.2 ± 2.95	20.8 ± 2.4	20.1 ± 2.1	20.3 ± 1.7
Nuclear diameter, μm	11.0 ± 1.09	11.3 ± 1.03	11.0 ± 1.2	11.2 ± 1.7
Hepatocyte area, μm²	324.3 ± 89.9	350.0 ± 79.4	317.1 ± 62.5	323.5 ± 71.2
Nuclear area, μm²	96.0 ± 18.6	101.7 ± 17.5	94.9 ± 16.1	98.5 ± 17.3
NCI	0.30 ± 0.02	0.28 ± 0.01	0.26 ± 0.02 **	0.28 ± 0.01

Note. Data are presented as M ± SD. Statistical significance of differences compared to the control group: *p < 0.05, ** p < 0.01, ***p < 0.001.

Changes in Six-Month-Old Animals. At six months of age, the absolute liver mass did not differ among the studied groups (Table 3). At the same time, the relative liver mass remained significantly higher in the embryonic (p = 0.005) and pre-fetal (p = 0.008) exposure groups compared to the control. The diameter and area of hepatocytes, as well as their nuclear dimensions, exhibited no statistically significant differences among the groups (all p > 0.05).

The nuclear-cytoplasmic index was significantly lower than the control values in the pre-fetal and fetal exposure groups (p < 0.01).

Table 3

Liver morphometric parameters in six-month-old offspring under normal development and after prenatal hypoxia at different stages of embryogenesis

Morphometric indicator	Control (n=10)	Embryonic period (n=10)	Pre-fetal period (n=10)	Fetal period (n=10)
Absolute liver mass, mg	9583 ± 421.5	9250 ± 160.4	9373 ± 179.6	9271 ± 212.2
Relative liver weight, %	3.72 ± 0.09	3.87 ± 0.07 **	3.85 ± 0.01 **	3.73 ± 0.03
Hepatocyte diameter, µm	22.67 ± 2.1	22.83 ± 1.8	22.71 ± 2.1	22.80 ± 2.0
Nuclear diameter, µm	12.3 ± 0.82	12.6 ± 1.24	12.3 ± 1.14	12.2 ± 1.7
Hepatocyte area, µm²	406.0 ± 74.8	409.1 ± 83.1	404.9 ± 71.6	408.1 ± 73.8
Nuclear area, µm²	119.8 ± 16.7	124.6 ± 17.9	118.7 ± 16.7	116.8 ± 14.5
NCI	0.30 ± 0.01	0.30 ± 0.02	0.28 ± 0.01 **	0.28 ± 0.01 **

Note. Data are presented as M ± SD. Statistical significance of differences compared to the control group: *p < 0.05, **p < 0.01, ***p < 0.001.

Histological examination of the livers from the animals in the experimental groups revealed persistent sinusoidal dilation and signs of venous congestion (Fig. 1D).

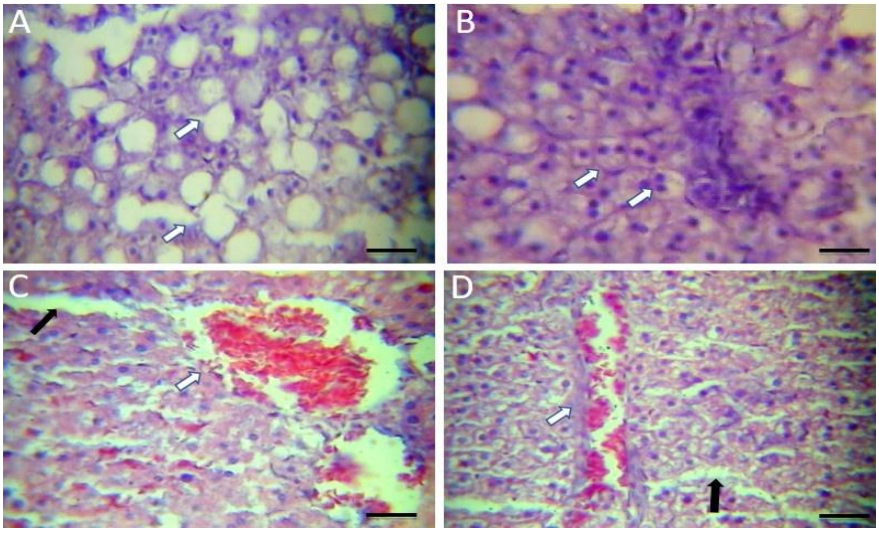

Figure 1

Representative photomicrographs of liver tissue in rats exposed to prenatal hypoxia: (A) hydropic vacuolization of hepatocytes and (B) binucleated hepatocytes in 1-month-old animals; (C) sinusoidal dilatation and blood stasis in 3-month-old animals; (D) sinusoidal dilatation and blood stasis in 6-month-old animals. Hematoxylin and eosin staining. Scale bars = 50 µm.

Hemostasis Parameters

One-Month-Old Animals. At one month of age, the fibrinogen concentration was significantly lower than the control values in all experimental groups ($p < 0.001$) (Fig. 2). The lowest values were recorded in the embryonic exposure group. Intergroup differences were also statistically significant ($p < 0.001$). The aPTT values in all experimental groups exceeded the control values ($p < 0.001$) (Fig. 3). The maximum values were registered in the animals of the embryonic exposure group. Plasma tolerance to heparin was also significantly higher than the control level in all experimental groups (p

< 0.001) (Fig. 4). However, there were no differences among the embryonic, pre-fetal, and fetal exposure groups ($p > 0.05$).

Three-Month-Old Animals. By three months of age, the fibrinogen concentration in all experimental groups exceeded the control values ($p < 0.001$); however, no differences were detected among the experimental groups. The aPTT value remained significantly lower than the control level in all prenatal hypoxia groups ($p \leq 0.006$). Analysis of plasma tolerance to heparin revealed statistically significant differences among the groups (Welch's ANOVA, $p < 0.001$). In the embryonic and pre-fetal exposure groups, the values of this parameter were lower than those of the control, whereas no statistically significant differences from the control were observed in the fetal exposure group.

Six-Month-Old Animals. At six months of age, the fibrinogen concentration remained above the control level in all experimental groups ($p < 0.001$). The maximum values were recorded in the animals of the fetal exposure group. The aPTT value in all experimental groups remained lower than the control values. The lowest values were found in the embryonic exposure group, which differed significantly from the other experimental groups ($p < 0.001$). Plasma tolerance to heparin was reduced in all prenatal hypoxia groups compared to the control (Welch's ANOVA, $p < 0.001$). Furthermore, statistically significant differences were identified among all experimental groups: the maximum values were noted in the embryonic exposure group, while the minimum values were in the fetal exposure group.

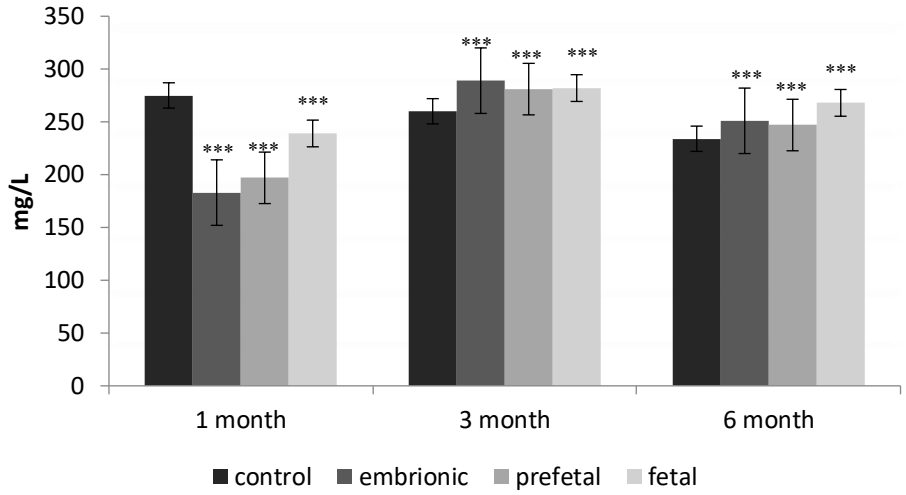

Figure 2
Age-related changes in plasma fibrinogen concentration in offspring rats after prenatal hypoxia

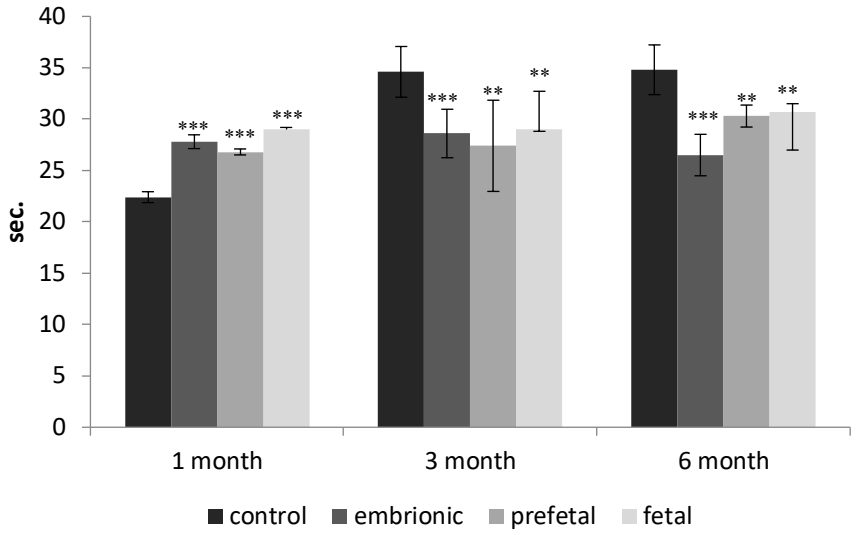

Figure 3
Age-related changes in activated partial thromboplastin time (aPTT) in offspring rats after prenatal hypoxia

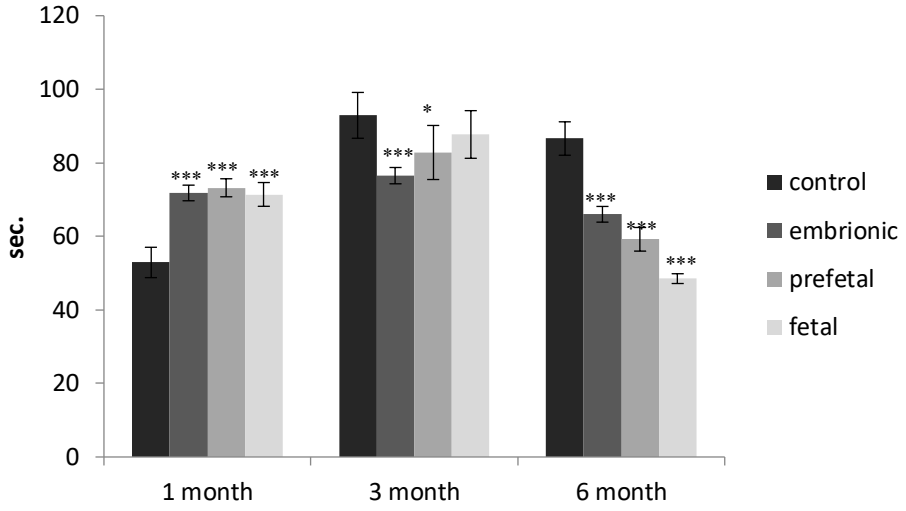

Figure 4
Age-related changes in plasma heparin tolerance (PHT) in offspring rats after prenatal hypoxia

Discussion

The main finding of the present study is the identification of the biphasic nature of postnatal adaptation of the liver and hemostatic system to severe prenatal hypoxia. The obtained data indicate an age-related inversion of the coagulation profile in rat offspring—a transition from early hypocoagulation to a persistent procoagulant state in adulthood. The findings suggest that this condition is associated with persisting histological signs of intrahepatic microvascular bed dilation, which remains even against the background of substantial, albeit incomplete, morphometric recovery of the parenchyma.

Our results expand upon the classical DOHaD (Developmental Origins of Health and Disease) concept (Gluckman et al., 2016). It has been previously shown that prenatal hypoxia is associated with long-term metabolic, cardiovascular, and neuroendocrine disorders in offspring (Sutovska et al., 2022). However, the present data indicate that the consequences of prenatal hypoxia affect not only

the hepatic parenchyma but also the vascular component of the liver. Based on the obtained findings, a two-stage hypothetical model for the pathogenesis of the identified disorders can be proposed.

During the first month of life, the most obvious consequence of the experienced hypoxia was severe liver hypoplasia (the organ mass deficit was 19–25%). The mass reduction was combined with hydropic degeneration of hepatocytes, which is a classic consequence of hypoxic injury associated with impaired energy metabolism and water-electrolyte balance (Kumar et al., 2020). The obtained morphometric data may indicate the activation of compensatory mechanisms: hepatocyte hypertrophy, an increase in the nuclear-cytoplasmic index, and the formation of binucleated cells. These features reflect the activation of polyploidization processes—an evolutionarily conserved mechanism for rapid adaptation and functional mass increase without complete mitosis (Donne et al., 2021). Nevertheless, this structural immaturity translates directly into a functional deficit. The systemic hypocoagulation recorded in one-month-old animals (decreased fibrinogen levels, prolonged aPTT) is logically explained by the suppression of the protein-synthetic activity of immature hepatocytes.

By three and six months of age, hepatocyte sizes and their nuclear parameters had largely approached the control values. Although the sizes of most cells and nuclei normalized, persistent changes in the nuclear-cytoplasmic ratio were recorded in some groups. Nonetheless, the observed dynamics confirm the significant regenerative potential of the liver, ensuring the restoration of parenchymal cellular homeostasis (Ma et al., 2025). However, the normalization of hepatocyte morphology was not accompanied by the restoration of the vascular component. In adult animals, the persistence of sinusoidal dilation and venous stasis was histologically confirmed. The relative liver mass in certain experimental groups remained elevated. This aligns with current data indicating that the specific features of vascular network formation in the early neonatal period determine the final organ size and can contribute to its long-term remodeling (Azizoglu et al., 2025, Brancatelli et al., 2018, Haddadin et al., 2024).

Particular attention should be given to the identified association between persistent sinusoidal dilation and the development of hypercoagulation in adult rats (increased fibrinogen levels, shortened aPTT, decreased plasma tolerance to heparin). Similar long-term impairments in hemostatic regulation following antenatal hypoxic exposure have been previously described in both experimental and clinical studies (Tsauosi et al., 2023, Jafarova, 2023); however, the mechanisms maintaining them remain a subject of debate. Liver sinusoidal endothelial cells (LSECs) act as key regulators of vascular tone and homeostasis (Gracia-Sancho et al., 2021, Qu et al., 2024). Chronic alterations in sinusoidal architecture can disrupt endothelial mechanosensitivity and attenuate its anticoagulant properties (Gao et al., 2024). Histological signs of venous stasis may reflect local hemodynamic disturbances. According to the literature, such architectural changes are consistent with the development of LSEC dysfunction and local hypoxia (Gao et al, 2024), which is hypothesized to act as a prothrombotic trigger mediating systemic hypercoagulation (Ortega-Ribera et al, 2023). In this context, the progressive decrease in plasma tolerance to heparin may align with the hypothesis of weakened endothelial anticoagulant properties.

Despite the general trend of the changes, individual parameters varied depending on the timing of the intrauterine hypoxic exposure. This confirms the existence of specific "windows of vulnerability" in the developing liver and requires targeted investigation in future studies. The limitations of this study include the lack of direct molecular assessment of LSEC dysfunction markers and angiocrine signaling. Future work should focus on deciphering the specific molecular cascades (including, for example, the HIF-1α signaling pathway) (Qing et al., 2024) linking vascular remodeling to hemostatic complications.

Conclusion

Thus, the study results demonstrate that prenatal hypoxia induces a biphasic adaptive response involving early liver hypoplasia and hypocoagulation, followed by the recovery of hepatocyte morphometric characteristics but with the persistence of vascular remodeling signs and the development of a procoagulant phenotype. The obtained data suggest that long-term impairments of hepatic microcirculation may serve as a crucial link connecting intrauterine hypoxic exposure with delayed hemostatic disorders in adulthood.

References

Azizoglu, D. B., Perez, K., Zheng, S. L., Rahman, S., Rim, E. Y., Anbarchian, T., Fish, M., Loh, K. M., Red-Horse, K., & Nusse, R. (2025). Vascularization of neonatal liver lobules presages adult liver size. *Nature Communications, 16*(1), 9989. https://doi.org/10.1038/s41467-025-64930-w

Brancatelli, G., Furlan, A., Calandra, A., & Dioguardi Burgio, M. (2018). Hepatic sinusoidal dilatation. *Abdominal Radiology, 43*(8), 2011–2022. https://doi.org/10.1007/s00261-018-1465-8

Cao, L., Wang, J., Bo, L., Li, D. W., Yin, N., Zhou, A. W., & Mao, C. P. (2019). Effects of hypoxia on the growth and development of the fetal ovine hepatocytes in primary culture. *Biomedical and Environmental Sciences, 32*(8), 592–601. https://doi.org/10.3967/bes2019.077

Donne, R., Sangouard, F., Celton-Morizur, S., & Desdouets, C. (2021). Hepatocyte polyploidy: Driver or gatekeeper of chronic liver diseases. *Cancers, 13*(20), 5151. https://doi.org/10.3390/cancers13205151

Ducsay, C. A., Goyal, R., Pearce, W. J., Wilson, S., Hu, X. Q., & Zhang, L. (2018). Gestational hypoxia and developmental plasticity. *Physiological Reviews, 98*(3), 1241–1334. https://doi.org/10.1152/physrev.00043.2017

Gao, J., Lan, T., Kostallari, E., Guo, Y., Lai, E., Guillot, A., Ding, B., Tacke, F., Tang, C., & Shah, V. H. (2024). Angiocrine signaling in sinusoidal homeostasis and liver diseases. *Journal of Hepatology, 81*(3), 543–561. https://doi.org/10.1016/j.jhep.2024.05.014

Gao, J., Zuo, B., & He, Y. (2024). Liver sinusoidal endothelial cells as potential drivers of liver fibrosis. *Molecular Medicine Reports, 29*(3), Article 40. https://doi.org/10.3892/mmr.2024.13164

Gluckman, P. D., & Hanson, M. A. (2016). The developmental origins of health and disease (DOHaD) concept: Past, present and future. In C. S. Rosenfeld (Ed.), *The epigenome and developmental origins of health and disease* (pp. 1–15). Academic Press. https://doi.org/10.1016/B978-0-12-801383-0.00001-3

Graf, A. V., Maslova, M. V., Artiukhov, A. V., Ksenofontov, A. L., Aleshin, V. A., & Bunik, V. I. (2022). Acute prenatal hypoxia in rats affects physiology and brain metabolism in the offspring, dependent on sex and gestational age. *International Journal of Molecular Sciences, 23*(5), 2579. https://doi.org/10.3390/ijms23052579

Gracia-Sancho, J., Caparrós, E., Fernández-Iglesias, A., & Francés, R. (2021). Role of liver sinusoidal endothelial cells in liver diseases. *Nature Reviews Gastroenterology & Hepatology, 18*(6), 411–431. https://doi.org/10.1038/s41575-020-00411-3

Haddadin, R., Aboujaoude, C., & Trad, G. (2024). Congestive hepatopathy: A review of the literature. *Cureus, 16*(4), e58766. https://doi.org/10.7759/cureus.58766

Jafarova, G. G. (2023). Status of coagulation system in adolescent rats exposed to hypoxia during prenatal development. *Azerbaijan Journal of Physiology, 38*(1), 19–24. https://doi.org/10.59883/ajp.51

Korzhevskiy, D. E., & Gilyarov, A. V. (2010). *Osnovy gistologicheskoy tekhniki*. SpetsLit.

Kumar, V., Abbas, A. K., & Aster, J. C. (2020). *Robbins & Cotran pathologic basis of disease* (10th ed.). Elsevier.

Ma, X., Huang, T., Chen, X., Li, Q., Liao, M., Fu, L., Huang, J., Yuan, K., Wang, Z., & Zeng, Y. (2025). Molecular mechanisms in liver repair and regeneration: From physiology to therapeutics. *Signal Transduction and Targeted Therapy, 10*(1), 63. https://doi.org/10.1038/s41392-024-02104-8

Matsumoto, T. (2022). Implications of polyploidy and ploidy alterations in hepatocytes in liver injuries and cancers. *International Journal of Molecular Sciences, 23*(16), 9409. https://doi.org/10.3390/ijms23169409

McGuckin, M. M., Wang, D., Ortiz, J., Dobrinskikh, E., Tong, W., Botting-Lawford, K. J., Niu, Y., Giussani, D. A., & Wesolowski, S. R. (2025). Hypoxic pregnancy promotes fibrosis and increases stress metabolites in the ovine fetal liver. *The Journal of Physiology, 603*(10), 3223–3243. https://doi.org/10.1113/JP288724

Ortega-Ribera, M., Gibert-Ramos, A., Abad-Jordà, L., Magaz, M., Téllez, L., Paule, L., Castillo, E., Pastó, R., de Souza Basso, B., Olivas, P., Orts, L., Lozano, J. J., Villa, R., Bosch, J., Albillos, A., García-Pagán, J. C., & Gracia-Sancho, J. (2023). Increased sinusoidal pressure impairs liver endothelial mechanosensing, uncovering novel biomarkers of portal hypertension. *JHEP Reports, 5*(6), 100722. https://doi.org/10.1016/j.jhepr.2023.100722

Prus, R., Appelhans, O., Logash, M., Pokotylo, P., Nowicki, G. J., & Ślusarska, B. A. (2021). Histological and morphometric assessment of the adult and juvenile rat livers after mild traumatic brain injury. *Cells, 10*(5), 1121. https://doi.org/10.3390/cells10051121

Qing, Z., Luo, Q., Duan, J., Lin, J., Huang, H., Yang, S., & Zeng, Z. (2024). SENP1 attenuates hypoxia–reoxygenation injury in liver sinusoidal endothelial cells via the HIF-1α signaling pathway. *Molecular Medicine Reports, 29*(4), Article 64. https://doi.org/10.3892/mmr.2024.13188

Qu, J., Wang, L., Li, Y., & Li, X. (2024). Liver sinusoidal endothelial cell: An important yet often overlooked player in liver fibrosis. *Clinical and Molecular Hepatology, 30*(3), 303–325. https://doi.org/10.3350/cmh.2024.0022

Salyha, N., & Oliynyk, I. (2023). Hypoxia modeling techniques: A review. *Heliyon, 9*(2), e13238. https://doi.org/10.1016/j.heliyon.2023.e13238

Smith, K. L. M., Swiderska, A., Lock, M. C., Graham, L., Iswari, W., Choudhary, T., Thomas, D., Kowash, H. M., Desforges, M., Cottrell, E. C., Trafford, A. W., Giussani, D. A., & Galli, G. L. J. (2022). Chronic developmental hypoxia alters mitochondrial oxidative capacity and reactive oxygen species production in the fetal rat heart in a sex-dependent manner. *Journal of Pineal Research, 73*(3), e12821. https://doi.org/10.1111/jpi.12821

Sutovska, H., Babarikova, K., Zeman, M., & Molcan, L. (2022). Prenatal hypoxia affects foetal cardiovascular regulatory mechanisms in a sex- and circadian-dependent manner: A review. *International Journal of Molecular Sciences, 23*(5), 2885. https://doi.org/10.3390/ijms23052885

The jamovi project. (2024). *jamovi* (Version 2.6) [Computer software]. https://www.jamovi.org

Tsaousi, M., Iliodromiti, Z., Iacovidou, N., Karapati, E., Sulaj, A., Tsantes, A. G., Petropoulou, C., Boutsikou, T., Tsantes, A. E., & Sokou, R. (2023). Hemostasis in neonates with perinatal hypoxia: Laboratory approach: A systematic review. *Seminars in Thrombosis and Hemostasis, 49*(4), 391–401. https://doi.org/10.1055/s-0042-1758148

Vetrovoy, O., Stratilov, V., Nimiritsky, P., Makarevich, P., & Tyulkova, E. (2021). Prenatal hypoxia induces premature aging accompanied by impaired function of the glutamatergic system in rat hippocampus. *Neurochemical Research, 46*(3), 550–563. https://doi.org/10.1007/s11064-020-03191-z

Vetrovoy, O., Tyulkova, E., Stratilov, V., Baranova, K., Nimiritsky, P., Makarevich, P., & Rybnikova, E. (2020). Long-term effects of prenatal severe hypoxia on central and peripheral components of the glucocorticoid system in rats. *Developmental Neuroscience, 42*(2–4), 145–158. https://doi.org/10.1159/000512223

Zotova, A. B., Khramova, T. O., Sydorenko, R. V., Sherstiuk, S. O., & Panov, S. I. (2024). The influence of experimental chronic antenatal and acute postnatal hypoxia on the morphological state of the liver stromal component. *Open Access Macedonian Journal of Medical Sciences, 12*(3), 438–442. https://doi.org/10.3889/oamjms.2024.11940