

ПУТИ ФАРМАКОЛОГИЧЕСКОЙ КОРРЕКЦИИ СИНДРОМА ЗАДЕРЖКИ РОСТА ПЛОДА

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Цель. Сравнительный анализ эффективности фармакологической коррекции синдрома задержки роста плода (СЗРП) монотерапией диосмином и дипиридамолом.

Материалы и методы. Проведено ретроспективное и проспективное обследование 80 беременных женщин с одноплодной беременностью на сроке гестации от 28 до 36 недель с подтвержденным диагнозом СЗРП 1 или 2 степени ассиметричной формы. Беременные женщины, принимавшие участие в исследовании, были на 75,0% среднего репродуктивного возраста (23-29 лет). Доля юных первородящих в I группе составила 10,0%, во II группе – 15,0%; возрастных первородящих – 17,5 и 10,0% соответственно. Был проведен расширенный сбор и анализ анамнеза, общеклинический и акушерско-гинекологический осмотр, лабораторные и ультразвуковые методы. Новорожденных оценивали по шкале Апгар при рождении и через 5 мин. В раннем неонатальном периоде оценивали врожденные и проходящие патологические синдромы.

Результаты. У пациенток, получавших диосмин ($n=40$), достигнуто снижение индекса резистентности правой и левой маточных артерий до $0,440 \pm 0,004$ и $0,460 \pm 0,004$ соответственно, для артерии пуповины – до $0,56 \pm 0,02$, что ниже, чем в группе пациенток, принимавших дипиридамолом ($n=40$). Выявлено положительное влияние диосмина на внутриутробное состояние плода, реализующееся в виде увеличения его компенсаторных способностей для адаптации к хронической гипоксии достоверно в большем проценте случаев по сравнению с дипиридамолом. После завершения фармакологической коррекции выявлена тенденция к нормализации основных показателей системы гемостаза в большем проценте случаев среди пациенток, принимавших диосмин. Это, в свою очередь, благоприятно сказалось на объеме кровопотери при физиологических родах. Так в I группе среднее количество теряемой крови составило 180 ± 15 мл, тогда как во II группе – 265 ± 15 мл ($p < 0,05$). Однако, при оперативном родоразрешении таких различий получено не было. В I группе сразу после родоразрешения 10,0% новорожденных были переведены в отделение реанимации и интенсивной терапии, во II группе перевод в реанимационное отделение потребовался 37,5% детям ($< 0,05$). Всех остальных детей сразу после рождения переводили в удовлетворительном состоянии на совместное пребывание с матерью, и они не требовали реанимационных мероприятий.

Заключение. Показано увеличение компенсаторных способностей плода в условиях хронической внутриутробной гипоксии достоверно в большем проценте случаев после фармакологической коррекции диосмином. Это, в свою очередь, благоприятно сказалось на перинатальных исходах, рождении детей с большим массо-ростовым показателем и индексом здоровья.

Ключевые слова: синдром задержки роста плода; диосмин; дипиридамолом; ангиопротектор.



METHODS OF PHARMACOLOGICAL CORRECTION OF INTRAUTERINE GROWTH RESTRICTION SYNDROME

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Aim. Comparative analysis of the effectiveness of pharmacological correction of intrauterine growth restriction syndrome (IGRS) by monotherapy with diosmin and dipiridamol.

Materials and Methods. Retrospective and prospective examination of 80 pregnant women with singleton pregnancy with gestational age from 28 to 36 weeks with confirmed diagnosis of IGRS of 1 or 2 degree asymmetric form was conducted. 75.0% Of pregnant women that participated in the study, were of the average reproductive age (23-29 years of age). The share of young first-time-mother in I group was 10.0%, in II group – 15.0%, the share of age first-time-mothers was 17.5 and 10.0%, respectively. Extended history taking and history analysis, general clinical and obstetric-gynecological examination were conducted, laboratory and ultrasound methods were used. Newborns were evaluated on Apgar scale at birth and in 5 minutes. In the early neonatal period, inborn and transient pathological syndromes were evaluated.

Results. In patients receiving diosmin (n=40), reduction of the resistance index of the right and left uterine arteries to 0.440 ± 0.004 and 0.460 ± 0.004 , respectively, and of the umbilical artery to 0.56 ± 0.02 was achieved, that is lower than in the group of patients taking dipiridamol (n=40). A positive influence of diosmin on the intrauterine condition of the fetus was found that was manifested by its increased compensatory capacities for adaptation to chronic hypoxia in reliably higher percent of cases as compared to dipiridamol. After pharmacological correction, a tendency to normalization of the main parameters of the system of hemostasis was found in higher percent in women taking diosmin. This, in turn, produced a favorable influence on the volume of blood loss in physiological deliveries. Thus, in I group the average amount of blood loss was 180 ± 15 ml, while in II group it was 265 ± 15 ml ($p < 0.05$). However, in operative delivery no such differences were obtained. In I group immediately after deliveries 10.0% of newborns were transferred to the resuscitation and intensive care unit, in II group transfer to resuscitation department was required in 37.5% of infants (< 0.05). All the rest of children immediately after birth in the satisfactory condition were placed to one ward with mother, and they did not require resuscitation measures.

Conclusion. Increase in the compensatory capacities of the fetus was shown in the conditions of chronic intrauterine hypoxia in a reliably higher percent of cases after pharmacological correction with diosmin. This, in turn, produced a favorable influence on perinatal outcomes, birth of children with a higher parameters of mass and height and health index.

Keywords: *intrauterine growth restriction syndrome; diosmin; dipiridamol; angioprotector.*

Pathological intrauterine condition of fetus represented by reduction of the growth rate relative to the gestational norm due to insufficient supply of nutrients and oxygen – intrauterine growth restriction syndrome (IGRS) – is one of the leading causes of perinatal morbidity and mortality. Retarded intrauterine formation of fetus further leads to retardation of mental and somatic development

of the child. Treatment and adaptation of such children includes use of complex costly measures to support the main parameters of their health and socialization [1-3].

Treatment and prophylaxis of IGRS remains an important issue even despite the continuous work of scientists and practitioners on this problem for many years with use of medicinal approaches. The conducted analysis

showed that 92% of pregnant females received certain medical drugs (MD) at different gestational ages [4-6].

With this aim, MD are discussed that can improve uteroplacental and fetoplacental circulation, normalize rheological and coagulation parameters of blood, improve the tone of vessel walls – angioprotectors that are actively used by obstetricians-gynecologists in their everyday work. Besides, these MD possess a general spasmolytic activity, ability to vasodilatation and to improvement of microcirculation. MD of angioprotector group are classified to two classes by origin: plant-based and synthetic. Plant-based preparations are safer and practically possess no side effects except individual intolerance.

One of such preparations that has been in used since 2006, is monocomponent diosmin (Flebodia 600) which was exposed to special treatment by coaggregation to increase its bioavailability and pharmaceutical effectiveness in relation to vessels. Diosmin reduces permeability of the vessel wall, suppresses production of free radicals, of thromboxane and prostaglandins participating in thrombus formation, and possesses anti-inflammatory properties. It is allowed to be used in pregnancy, since experimental and clinical trials did not show any embryotoxic, mutagenic and teratogenic action. A high degree of purification from intermediate products leads to minimization and extremely rare occurrence of side effects of therapy [2,8].

Another angioprotector drug permitted for use in pregnancy, is dipiridamol. Its main pharmacological effect consists in improvement of microcirculation through reduction of permeability of blood vessel walls and increase in the rate of metabolism in it. Besides, this drug reduces viscosity of blood, prevents adhesion of platelets and of other blood cells to the endothelium. Dipiridamol produces a preventive effect in relation to ischemia and hypoxia of tissues possessing a vasodilating capacity [9].

Aim – comparative analysis of efficiency of pharmacological correction of intrauterine growth restriction syndrome with diosmin and dipiridamol monotherapy.

Materials and Methods

A retrospective and prospective examination of 80 pregnant women was conducted. In the given work pharmacological efficiency of medical drugs allowed for use by Health Ministry of Russia was studied, in which connection permission of the regional ethic committee of Kursk Medical University was obtained for implementation of the study (protocol of the meeting of the regional ethic committee №2 of 18.02.2013).

The criteria of inclusion were: singlet pregnancy with gestational age from 28 to 36 weeks, confirmed diagnosis of chronic fetoplacental insufficiency, 1 and 2 degree IGRS, asymmetric form of fetal growth restriction. Criteria of exclusion: multifetal pregnancy, 3 degree fetal growth restriction syndrome, symmetric form of fetal growth restriction, extragenital pathology in a pregnant woman in decompensated stage, diagnosed malformations of fetus.

The patients were randomly divided to 2 clinical groups. After confirmation of the voluntary informed consent to participation in the study, patients of I group (n=40) were given diosmin perorally at a dose 600 mg once a day in the morning before meal within 4 weeks; patients of II group (n=40) were given dipiridamol 25 mg 3 times a day within 4 weeks.

75.0% of pregnant women that participated in the study, were of average reproductive age (23-29 years old). A share of young first-time-mothers in I group was 10.0%, in II group – 15.0%, the share of age first-time-mothers was 17.5 and 10.0%, respectively. To note, a group of scientists headed by E.V. Prodanova had the same age groups of women in their study (2011) [8].

On the basis of analysis of history data, somatic and obstetric-gynecological status, the studied groups could be considered comparable (p for all comparable parameters >0.05).

All patients of 28-36-week gestational age underwent ultrasound examination (US) with seven days interval for evaluation of the condition of fetoplacental complex. The first examination was conducted on admission to the hospital (Figure 1). The condition of the

fetus, of placenta, amniotic fluid were evaluated. The second and subsequent ultrasound examinations were conducted every seven

days for dynamic control of the condition of the fetus, of placenta, amniotic fluid with pharmacological correction.

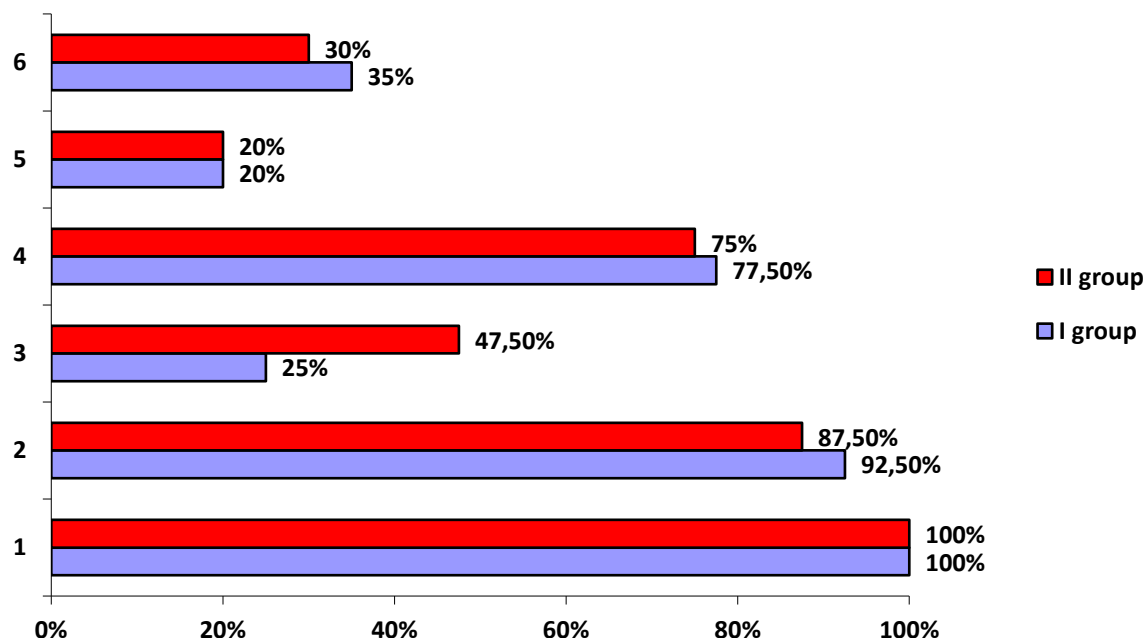


Fig. 1. Ultrasound examination of pregnant females on admission to hospital:
 1 – fetal growth restriction syndrome; 2 – expansion of intervillous space;
 3 – calcinosis of placenta; 4 – premature maturation of placenta;
 5 – hypoplasia of placenta; 6 – placentomegaly

By the results of US examination, patients of both groups were comparable ($p>0.05$). L.S. Logutova, et al. (2010) diagnosed all the women included into the study, with expansion of the intervillous space with rheological disorders in them, and with premature aging and calcinosis of placenta [3].

Doppler velocimetry of uteroplacental and fetoplacental blood flow was performed in all pregnant women on admission to hospital to make a correct diagnosis, and further each seven days for dynamic observation of changes in the blood flow in the arteries of uterus, umbilical cord and fetus. On the first ultrasound examination, increase in resistance index of uterine and umbilical arteries was diagnosed that indicated disturbances in the blood flow in fetoplacental complex. It is possible to speak about intrauterine hypoxia of

fetus and probable formation of IGRS in case of increase in resistance index of uterine arteries on both sides.

Besides, for evaluation of the intrauterine condition of fetus, antenatal cardiotocography was used after 30 weeks. Non-stress test was considered positive in case two and more accelerations with amplitude at least 15 beats per minute within 40 minutes of observation were recorded.

Before therapy, hemostasiogram was taken in all patients to study the main parameters of the system of hemostasis.

Statistical methodology included parametric (Student's test) and non-parametric (Wilcoxon test) methods used in calculations of quantitative changes in one group before and after treatment. Reliability of differences between groups was evaluated using Mann-

Whitney test. The obtained results were presented as arithmetic mean (M) \pm error of mean (m). Statistically significant for all parameters was considered reliability criterion $p < 0.05$.

Results and Discussion

In Figure 2 the results of the fourth ultrasound examination performed immediately after pharmacological correction of IURS with diosmin and dipiridamol are presented.

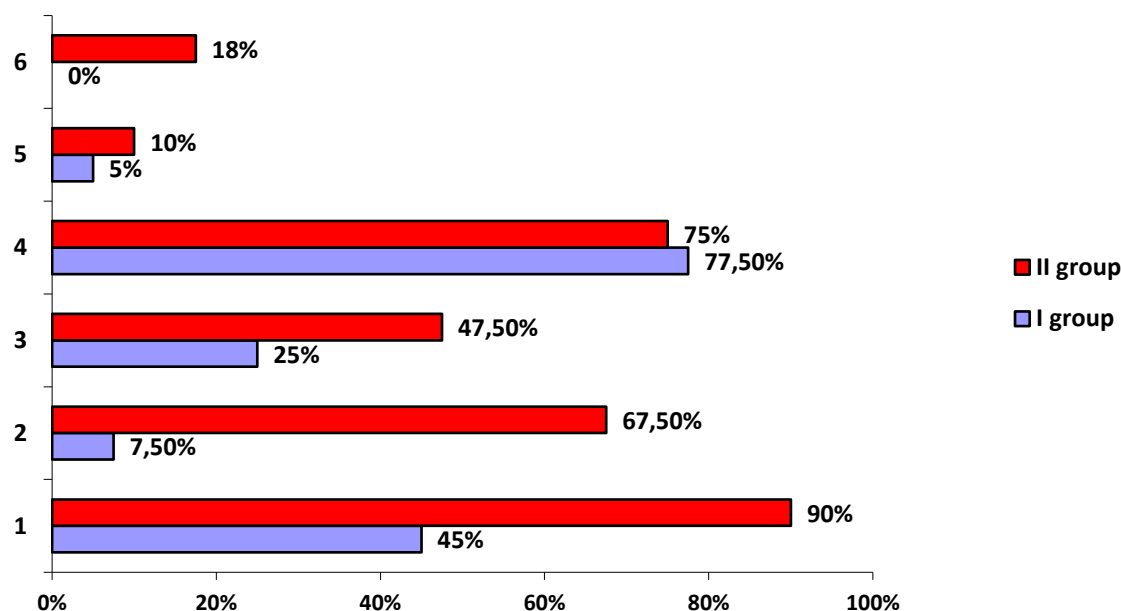


Fig. 2. Ultrasound examination of pregnant women after pharmacological correction:

- 1 – fetal growth retardation syndrome; 2 – expansion of intervillous space;
 3 – calcinosis of placenta; 4 – premature maturation of placenta;
 5 – hypoplasia of placenta; 6 – placentomegaly

Analysis of the obtained results revealed positive dynamics in both groups of study. However, a higher efficiency of medicinal therapy was recorded in the first group. In patients receiving diosmin, not a single case of placentomegaly was recorded, congestive phenomena were absent in the intervillous space ($p < 0.05$), which improved microcirculation in the fetoplacental complex. Besides, in this group increase in the rate of normalization of the main fetometric parameters was diagnosed $p < 0.05$.

Fetoplacental insufficiency is characterized by increased resistance index of the umbilical artery which evidences impairment of compensatory-adaptive mechanisms of vital activity of fetus. In this stage, intrauterine hypoxia of fetus develops which steadily progresses if untreated. E.V. Prodanova, et al. in their work diagnosed hypodynamic disor-

ders of IA, IB and II degree in 100% of patients in the first Doppler velocimetry of fetoplacental system [8], which coincides with the results of our work. According to the data of L.S. Logutova, et al., in all fetuses with IGRS the resistance index of umbilical vessels was increased before the treatment, which also coincides with the results of our work [3].

According to the cardiotocography data, 100% of fetuses of the patients of the comparison groups with the underlying disorders of uteroplacental and fetoplacental blood flow were in the condition of chronic intrauterine hypoxia. In table 1 the data are presented obtained before and after treatment.

Thus, in both groups positive dynamics was recorded that was more expressed in I group (Table 1).

Table 1

***Cardiotocography and Non-Stress Test of Fetuses of Patients
of Groups of Study Before and After Treatment***

Cardiotocography Criteria	I Group, n=40		II Group, n=40	
	before treatment	after treatment	before treatment	after treatment
Baseline heart rate, beats per minute, M±m	129.3±10.2	142.2±11.3*	128.2±10.2	130.4±10.8 [#]
Oscillations amplitude, beats per minutes, M±m	8.2±0.6	10.8±0.8*	8.1±0.6	8.4±0.8 [#]
Oscillations frequency, per minute, M±m	4.6±0.4	8.2±0.6* [#]	4.3±0.3	7.8±0.6*
Accelerations, quantity in 60 min., M±m	2.4±0.2	4.1±0.3*	2.2±0.2	2.5±0.2 [#]
Decelerations, quantity in 60 min., M±m	—	—	—	—
Total score, points, M±m	7.3±0.6	9.1±0.7*	7.2±0.6	7.5±0.6 [#]
Reactive non-stress test, %	90.0%	97.5%	82.5%	92.5%
Areactive non-stress test test, %	10.0%	2.5%*	17.5%	7.5% ^{**}

Note: * – comparison with initial data, $p<0.05$); # – comparison of the data after treatment of both groups, $p<0.05$

Analysis of data of hemostasiogram showed hypercoagulation syndrome and hyperfibrinemia in the women participating in the study (Table 2). In the given case, the signs of hypercoagulation were increase in Quick prothrombin test and of fibrinogen above the upper reference values. Increase in the amount of D-dimer in blood evidences disorders in platelet hemostasis.

After completion of pharmacological correction a tendency to normalization of the main parameters of the system of hemostasis was found in higher percentage of patients taking diosmin. This, in its turn, decreased the volume of hemorrhage in physiological deliveries. Thus, in I group the amount of blood loss was 180 ± 15 ml, while in II group it was 265 ± 15 ml ($p<0.05$). However, in the surgical delivery no such differences were noted.

Table 2

Hemostasiogram of Patients of Groups of Study Before and After Treatment

Parameter	I Group, n=40		II Group, n=40	
	before treatment	after treatment	before treatment	after treatment
Fibrinogen, g/l, M±m	6.5±0.1	4.4±0.1*	6.1±0.1	5.7±0.1 [#]
Activated partial thromboplastin time, sec, M±m	27.2±0.1	34.6±0.1*	29.2±0.1	34.9±0.1
Quick prothrombin test, M±m	120.0±0.1	107.0±0.1*	124.0±0.1	119.0±0.1 [#]
D-dimer, g/l, M±m	854 ±10	528±10*	790±10	690±10 [#]

Note: * – comparison with initial data, $p<0.05$); # – comparison of data after treatment of both groups, $p<0.05$

Physiological deliveries were in 50.0% of women (n=20) in I group, and in 42.5% (n=17) in II group; preterm deliveries were in 20.0% (n=8) and 25.0% (n=10); term deliveries – in 80.0% (n=32) and 75.0% (n=30), respectively. The average delivery term in I group was 37.8 ± 0.7 weeks, in II group – 36.8 ± 0.8 weeks. L.S. Logutova, et al. reported 37% of vaginal

deliveries, all the rest of the women had abdominal deliveries in the planned and emergency order; indications to cesarean section included progressing form of fetoplacental insufficiency and acute intrauterine hypoxia of fetus [3].

The results of analysis of fetometric parameters of a child at birth are given in Table 3.

Table 3

Comparative Analysis of Fetometric Parameters of Child at Birth

Parameter	I Group, n=40	II Group, n=40	p
Weight at birth, g, M \pm m	2598.25 \pm 205.56	2180.75 \pm 180.44	<0.05
Height at birth, cm, M \pm m	48.80 \pm 3.86	42.68 \pm 3.43	<0.05
Head circumference, cm, M \pm m	33.05 \pm 2.61	29.55 \pm 2.50	<0.05
Chest circumference, cm, M \pm m	31.03 \pm 2.45	27.15 \pm 2.31	<0.05
Assessment on Apgar scale, points, M \pm m: at birth	7.50 \pm 0.59	6.95 \pm 0.55	<0.05
in 5 min.	8.20 \pm 0.65	7.65 \pm 0.62	<0.05

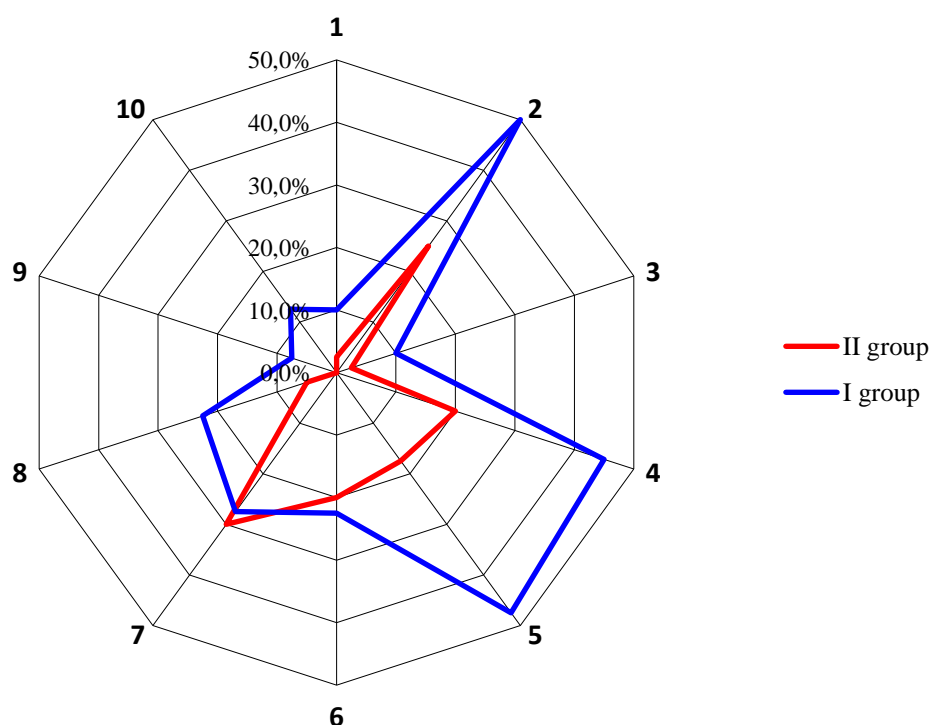


Fig. 3. Structure of perinatal morbidity:

1 – intranatal asphyxia; 2 – I degree cerebral ischemia; 3 – hypoxic-ischemic damage central nervous system injury; 4 – respiratory distress syndrome; 5 – intrauterine infection of unclear etiology; 6 – fetal type of circulation; 7 – physiological jaundice; 8 – conjugated jaundice; 9 – motor disorder syndrome; 10 – edematous syndrome

In I group immediately after deliveries 10.0% of newborns were transferred to resuscitation and intensive care unit, in II group 37.5% of children (<0.05) needed transfer to resuscitation. All the rest of the children in the satisfactory condition were placed together with the mother immediately after birth, and did not require any resuscitation measures.

The analysis of the structure of perinatal morbidity shows a large share of children with cerebral ischemia (Figure 3). This is a vivid demonstration of the situation when chronic intrauterine hypoxia of fetus was not compensated for during the pregnancy, and in the deliveries hypoxic lesion of the central nervous system developed in fetus.

Conclusion

Thus, the results obtained in the given study, demonstrate increase in the compensa-

tory capacities of fetus in conditions of chronic intrauterine hypoxia in reliably higher percentage of cases after pharmacological correction with diosmin. This, in turn, favorably influences perinatal outcomes, with birth of children with a higher mass-height parameter and health index.

This regularity can be attributed to the fact of improvement by diosmin of hemodynamic processes in the mother-placenta-fetus system, with equal improvement of the blood flow in the uterine and umbilical arteries, the aorta and the middle cerebral artery of fetus with proven reliability; it eliminates venous congestion in the intervillous space of fetoplacental system and, as the consequence, increases the delivery of oxygen and nutrients to the fetus, with subsequent increase in its compensatory-adaptive reactions.

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Дополнительная информация [Additional Info]

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