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PHARMACOLOGICAL CORRECTION OF FETOPLACENTAL INSUFFICIENCY WITH FETAL GROWTH RETARDATION SYNDROME

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Abstract

Introduction: fetoplacental insufficiency (FPI) is an important problem of obstetrics. This pathological condition leads to the development of fetal growth retardation syndrome (FGRS). Any standard treatment regimens cannot exist due to a combination of individual etiological factors and pathogenetic mechanisms of the development of this complication. Angioprotective drugs take the lead in the treatment, improving blood flow, coagulation and rheological properties of blood, tissue perfusion, and their supply with oxygen and nutrients.

Objectives: the aim of the study was to compare the pharmacological effectiveness of commonly used angioprotective agents «Pentoxifylline»®, «Phlebodia 600»,® and "Curantil 25»® based on the results of laboratory and instrumental methods of research conducted after treatment.

Methods: the retrospective and prospective survey of 120 pregnant women with 28-36 weeks of gestation were carried out on a clinical site of the Department of Obstetrics and gynecology of KSMU, and on the site of the Regional Perinatal Center of the City of Kursk.

Results: as a result of the study, there was developed and scientifically substantiated a variant of monotherapy of placental insufficiency with fetal growth retardation syndrome, using the drug «Phlebodia 600»®, aimed at improving the microcirculation in the system «mother-placenta-fetus» for the purpose of having children with a higher weight and growth parameters. It is recommended to take a course of 1 tablet (600 mg) per day in the morning, on an empty stomach, during 1 month.

Conclusions: the analysis of the results of the instrumental research methods after pharmacological correction revealed an equivalent improvement in hemodynamic parameters in both the uterine vessels and in the artery of the umbilical cord, which is due to the action of the preparation «Flebodia 600»®, whereas «Pentoxifylline»® has a partial positive effect on the uterine and placental blood flow, and «Kurantil 25»® predominantly affects the uterine blood flow.

Key words: fetoplacental insufficiency; fetal growth retardation syndrome; Flebodia 600; Curantil 25; Pentoxifylline; angioprotector; microcirculation.

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Introduction.

The use of medicines drugs during pregnancy is one of the least studied problems of clinical pharmacology. Due to ethical reasons for large clinical studies in pregnant women are not held. Cautions in packing in most cases provide instructions to use it during pregnancy only when the «benefit exceeds the risk», although this ratio estimate, without knowing the probability of undesirable drug effects on the fetus is not always easy. In addition, assigning drugs to pregnant women, doctors often forget that the physiological changes that occur in women, can lead to changes in the pharmacokinetics of the drug and, therefore, changes in their efficacy and safety, which is fraught with consequences not only for the fetus, but also mother [1, 2].

The results of the retrospective analysis of medical records, clinical observations, and opinion polls suggest that the drugs may play a much more important role in the occurrence of congenital

abnormalities, slowing fetal development and subsequent physical and intellectual development of a child than previously assumed [3].Theoretically, the ideal situation is a complete rejection of the use of drugs during pregnancy. However, this is not possible, because the pregnant women and the chronically ill, the abolition of drugs which is fraught with serious consequences for their health. In addition, during pregnancy and its complications arise new diseases that threaten the health and sometimes life of the woman and the fetus. Therefore, counseling a pregnant woman, a doctor in the appointment of drugs each time have to weigh the benefit/risk ratio, as recommended by the instructions for use of the drug. Unfortunately, in most cases, have to rely on their own clinical experience and intuition. The amount of information on this matter is negligible, and available – not systematized, and it is difficult to see [4, 5].

Recent studies have shown that the FPI is a symptom that accompanies almost all the complications of pregnancy and contributes to hypoxia and as a consequence of the formation of fetal growth retardation syndrome (FGRS) in 60% of cases. According to some authors, its frequency varies from 45% to 86%, and has a clear upward trend, perinatal morbidity reaches 700 ‰, and deaths 24.2-177.4 ‰ [6, 7, 8, 9].

Standard treatment regimens exist cannot be due to a combination of individual etiological factors and pathogenetic mechanisms of development of this complication. The selection of drugs should be carried out individually and differentially in each observation, taking into account the severity and duration of complications, etiological factors and pathogenetic mechanisms underlying this disease. Individual approaches require dosing regimen and duration of use. Care should be taken to eliminate the side effects of some drugs [10, 11].

Unfortunately, instead of the proclamation of the World Health Organization (WHO) at the end of the twentieth century postulate «Reduction in the amount of drugs in the treatment process in the XXI century», his first decade is characterized by the widespread use of drugs that are not proven to be effective [12].

Pharmacoepidemiological studies in Russia E.V. Eliseeva and E.A. Strizhenok, revealed that more than 40% of pregnant women appointed agents pose a potential risk to the fetus, and the average number of 11 different items [2, 13].

The lack of evidence of adverse impact on the state of the mother and fetus of certain drugs used often enough in pregnancy (along with the successful use in the national practice of traditional regimens for decades), does not allow at the moment to give them [2].

Failure to prove adverse effects of drugs on the fetus and the mother's body does not exclude them from the category of potentially hazardous for health. In addition to the positive impact of drugs on the course of pregnancy is possible both direct and indirect negative impact of drugs on the fetus [11, 12, 14].

One of the major pathogenetic mechanisms of FPI is a violation of utero-placental blood flow and fetoplacental blood flow, accompanied by an increase in blood viscosity, red blood cells and platelets hyperaggregation, disorder of microcirculation and vascular tone [10, 15]. In this regard, an important place in the treatment of occupied angioprotective drugs that improve blood flow, coagulation and rheological properties of blood, tissue perfusion, to supply them with oxygen and nutrients [16, 17, 18].

Based on the foregoing, it seems urgent to comparative evaluation of pharmacological efficacy of commonly used drugs angioprotective «Pentoxifylline»®, «Phlebodia 600»® and «Curantil 25»® on the results of laboratory and instrumental methods of investigation after the treatment.

Objective: To evaluate the effectiveness of pathogenetically substantiated pharmacological correction of fetoplacental insufficiency with fetal growth retardation syndrome by use of angioprotective drug on the basis bioflavonoid.

For the first time considered the use of the drug on the basis of angioprotective bioflavonoid «Phlebodia 600»® with the purpose of pharmacological correction of fetoplacental insufficiency to fetal growth retardation syndrome. For the first time, a comparative study of clinical, laboratory, ultrasound and dopplerometric performance after therapy angioprotective drugs «Pentoxifylline»®, «Curantil 25»® and «Phlebodia 600»®.

The materials and methods

General characteristics of the examined patients. On the clinical basis of the Department Obstetrics and Gynecology KSMU and the burden on the basis of «Regional perinatal center» of the city of Kursk in the period from 2012-2015 year a retrospective and prospective examinations 120 pregnant women in the gestation of 28 to 36 weeks. In the hospital patients have been diagnosed symptoms chronic fetoplacental insufficiency (CFPI) and fetal growth retardation syndrome (FGRS).

Inclusion criteria were: carrying singleton pregnancy on gestational age from 28 to 36 weeks; confirmed diagnosis CFPI; the presence of fetal growth retardation syndrome 1 and 2 degrees; asymmetrical form of fetal growth retardation;

tolerability study used in pharmaceuticals; a written consent to participate in ongoing research.

Exclusion criteria: multiple pregnancy; fetal growth retardation syndrome of 3 degrees; symmetrical form fetal growth retardation due to the high frequency of chromosomal abnormalities in fetuses and hopelessness correction of this pathology; extragenital pathology in pregnant women in the stage of decompensation, diagnosed fetal malformations.

All examined women were randomized by pre-stratification into 3 clinical groups: group I (40 patients) – received «Pentoxifylline»® intravenously drip in a dose of 100 mg in 200-400 ml of isotonic sodium chloride solution, 1 time per day 5-7 injections per course through; group II (40) – took «Phlebodia 600»® 1 tablet (600 mg) daily for 4 weeks; group III (40) – took «Curantil 25»® 1 tablet (25 mg) 3 times a day for 4 weeks.

All drugs were administered according to the guidelines outlined in the handbooks «Drugs» and «Russian register of medicines» (2010) and instructions on the use of drugs.

In connection with the study of the effectiveness of pharmacological agents approved for use by the Ministry of Health and Social Development of the Russian Federation, received permission to conduct research in the regional ethics committees (RECs) in the KSMU from 23.10.2012.

Obtain voluntary informed consent to participate in the study, all women.

It should be noted that the groups were comparable in age, social status, physical characteristics and obstetric and gynecological history, this current pregnancy.

The study used a medical history, general clinical and obstetric, biochemical and ultrasound methods. In postpartum placentas conducted pathological examination, bacteriological crops followed.

Newborn condition was assessed by clinical examination including details of the physical development of the child, Apgar score at birth and 5 minutes later. Also taken into account peculiarities of early neonatal period on the following parameters: weight loss, its recovery, the presence of pathological symptoms and complications during the newborn period of adaptation.

Laboratory research. For early detection of potential systemic diseases, pregnancy complications and signs of the suffering of the fetus with the modern methods of laboratory diagnostics (general analysis of blood and urine tests, blood chemistry, hemostasiogram, coagulation, bacterial inoculation of flora and direct microscopic study of discharge from the vagina, cervix and urethra). All pregnant women conducted a serological survey for the presence of Hbs-antigen, HIV infection and syphilis.

Instrumental methods of research. In the first trimester echographic visual assessment of the elements of the ovum and the pregnant uterus was carried out using an ultrasonic device «Philips – HD11XE Ultrasound System» (Netherlands). In early pregnancy ultrasound diagnosis was carried out using two standard techniques (transvaginal and transabdominal). Visual assessment of the elements of the ovum was carried out in a two-dimensional echographic mode and included the definition of the shape and dimensions of the ovum, the measurement of the average inner diameter and volume of the ovum. Condition of the pregnant uterus was assessed by the local thickness of the myometrium hypertonus, the structure and size of the decidua tissue, as well as by the presence of retrochorial hematoma.

In the second and third trimesters were measured main indicators of fetus and assess their compliance with the gestational age; assessment of fetal life; estimate of the amount and composition of the amniotic fluid; the location, thickness and structure of the placenta [19].

Doppler study of uterine-placental-fetal blood flow was performed using an ultrasonic device «Philips – HD11XE Ultrasound System» (Netherlands), equipped with a doppler unit. The study was conducted with a frequency sensor convex 3.5 MHz.

Cardiotocographic study (CTG) study was conducted using the monitor «Sonicaid Team S 8000 care» (United Kingdom). CTG recording was carried out by indirect method with an external sensor located on the front of the abdominal wall of the mother. CTG recording was performed multiple times during the third trimester of pregnancy.

Morphological examination of placentas. Morphologic Subsequent studies used a macroscopic, morphometric and histological methods. Assessment of the severity of dystrophic and involutive-compensatory and adaptive processes in the placenta were given according to their degree of severity as the high, medium and low. Histological features CFPI thought: slowing the maturation and differentiation of the villi; dissociated development of villous tree; hyperplasia of the vascular wall and fibrosis of the stroma of the villi; prevalence of involution-dystrophic changes of compensatory-adaptive reactions in the placenta [20].

Statistical analysis of the results. Statistical data processing was carried out using standard packages Exel applications (Microsoft, 2007), STATISTICA 10.0 (Stat Soft). In calculating the quantitative changes that have occurred in the same group before and after treatment were used parametric (Student's t-test) and nonparametric (Wilcoxon test) methods.

Assessment of the significance of differences between the groups performed using the Mann-Whitney U-test. The results were expressed as the arithmetic mean of the form (M) ± error of the mean (m). A statistically significant for all parameters considered criterion reliability of p<0,05.

The results of research.

Age of surveyed patients ranged from 15 to 47 years and averaged for pregnant I group 26.78 ± 2.12; II group – 26.75 ± 2.12; III group – 24.98 ± 1.98. The overwhelming majority were women aged 21-29 years – 75.8% (91) (figure 1).

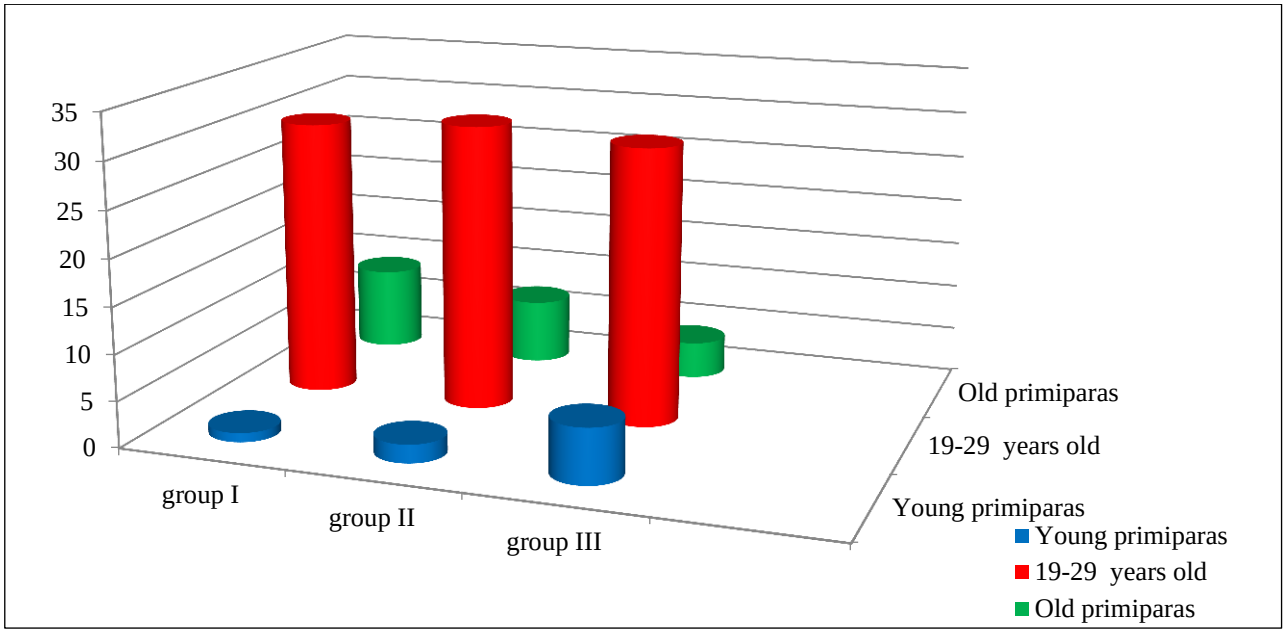

Fig. 1. Age characteristics of pregnant women

In the analysis of somatic pathology reliable differences in the examined groups were not identified. Every second woman had extragenital pathology (51.7%). Most frequent kidney disease and urinary tract. Chronic pyelonephritis with the same frequency occurs in 15% (6) of pregnant women in group I, 17.5% (7) of pregnant group II and 17.5% (7) of pregnant group III (p> 0.05).Chronic upper respiratory disease diagnosed at 5% (2) group I patients, at 7.5% (3) 10% and (4) patients of groups II and III, respectively. When analyzing the cardiovascular system revealed that hypertension suffered 17.5% (7) a group of women I, 10% (4) – II group and 12.5% (5) – III group.Varicosity veins of the lower extremities with equal frequency disease is diagnosed in pregnant I, II and III group: 5% (2) 7.5% (3) and 2.5% (1) pregnant women, respectively (p>0.05).

Study features of reproductive functions has shown that among the examinees in I, II and III groups multiparous predominated (65%, 75% and 70% respectively). The incidence of induced abortion on the woman's request or for medical and social reasons at different times for patients in the examined groups did not differ significantly and accounted for pregnant group I – 22.5% (9), II group – 30% (12), III group – 25% (10) (p>0.05). Moreover, high frequency operation ended in the previous pregnancy cesarean group I in 20% (8) women in group II at 15% (6) and III group, 20% (8) women. Premature birth history was identified in the group of pregnant I in 10% (4) and not significantly different from the frequency detecting pregnant groups II and III: 15% (6) 10% and (4), respectively (p> 0.05).Spontaneous abortions occurred in group I 5% (2) of the cases and did not differ significantly in frequency identification pregnant groups II and III: 5% (2) and 10% (4) cases, respectively (p> 0.05). Miscarrying pregnancies history was identified in a group of pregnant I 7.5% (3) and not significantly different from the frequency detecting pregnant groups II and III: 2.5% (1) and 5% (2), respectively (p>0.05). Reliably significant differences in the incidence of primary and secondary infertility in women's study groups have been identified.

Early toxemia of pregnant women suffering in group I 42.5% (17) that were not significantly different from these groups II and III: 30% (12)% and 35 (14), respectively (p>0.05). The threat of termination of pregnancy at different stages were diagnosed and treated in 57.5% (23) patients in group I, 40% (16) patients of group II and 42.5% (17) – III group. Anemia in pregnant women with equal frequency diagnosed 17.5% (7) group I patients, 25% (10) 17.5% (7) patients groups II and III, respectively. Polyhydramnios complicated during this pregnancy in 10% (4) of the cases in group I, 5% (2) in group II and 12.5% (5) cases in group III. Oligohydramnios was diagnosed in 27.5% (11) I

pregnant group 37.5% (15) 30% and (12) pregnant II and III groups, respectively, that the frequency does not differ significantly ($p>0.05$). Chronic fetoplacental insufficiency was diagnosed in all pregnant women who took part in the study.

The study of functional reserves of fetoplacental complex of all patients was performed by ultrasound, which included placentography, fetometry, assessment of amniotic fluid. Sonographic and Doppler study was performed in terms of 28 – 36 weeks of pregnancy. Ultrasound performed before treatment, revealed features shown in table 1.

Table 1

Structure and frequency of sonographic markers of fetoplacental insufficiency.

Indicators		Group I, abs. number (%)	Group II, abs. number (%)	Group III, abs. number (%)
Placenta with additional segments	28-30 weeks	1 (2.5)	1 (2.5)	2 (5.0)
	30-32 weeks	—	—	—
	32-34 weeks	—	—	—
	34-36 weeks	—	—	—
Placentomegaly	28-30 weeks	2 (5.0)	2 (5.0)	3 (7.5)
	30-32 weeks	3 (7.5)	5 (12.5)	2 (5.0)
	32-34 weeks	2 (5.0)	4 (10.0)	3 (7.5)
	34-36 weeks	4 (10.0)	3 (7.5)	4 (10.0)
Hypoplasia of placental	28-30 weeks	1 (2.5)	1 (2.5)	1 (2.5)
	30-32 weeks	1 (2.5)	4 (10.0)#	2 (5.0)
	32-34 weeks	3 (7.5)	1 (2.5)	2 (5.0)
	34-36 weeks	2 (5.0)	2 (5.0)	3 (7.5)
Premature maturation of placenta	28-30 weeks	2 (5.0)	2 (5.0)	4 (10.0)
	30-32 недель	2 (5.0)	10 (25.0)#	3 (7.5)&
	32-34 weeks	8 (20.0)	12 (30.0)	7 (17.5)&
	34-36 weeks	17 (42.5)	7 (17.5)#	16 (40.0)&
Calcinosis of placental	28-30 weeks	1 (2.5)	1 (2.5)	3 (7.5)
	30-32 weeks	2 (5.0)	1 (2.5)	2 (5.0)
	32-34 weeks	2 (5.0)	3 (7.5)	5 (12.5)
	34-36 weeks	7 (17.5)	5 (12.5)	9 (22.5)&
Expansion of the space intervillous	28-30 weeks	5 (12.5)	4 (10.0)	6 (15.0)
	30-32 weeks	4 (10.0)	12 (30.0)#	5 (12.5)&
	32-34 weeks	10 (25.0)	9 (22.5)	7 (17.5)
	34-36 weeks	15 (37.5)	12 (30.0)	17 (42.5)

Note: # – the significance of differences of indicators of comparison groups (differences were significant when comparing these two groups $p_{1-2}<0.05$);
& – the significance of the performance differences between the comparison groups (differences were significant when comparing these two groups $p_{2-3}<0.05$);
μ – the significance of differences of indicators of comparison groups (differences were significant when comparing these two groups $p_{1-3}<0.05$).

In assessing the scope and quality of amniotic fluid following regularities were revealed. This pathology is determined at 37.5% (15) group I patients, of whom 10% (4) in the form of moderate polyhydramnios amniotic fluid with an index of 185±25 mm, 27.5% (11) – in the form of moderate oligohydramnios amniotic fluid with an index of 110±10 mm. In group II 5% (2) women diagnosed with moderately severe polyhydramnios amniotic fluid index 187±23 mm, 37.5% (15) – in the form of moderate oligohydramnios amniotic fluid index 111±11 mm. In group III 12.5% (5) pregnant revealed moderately expressed hydramnion amniotic fluid index 189±23 mm, 30% (12) – in the form of moderate oligohydramnios amniotic fluid index 111±11 mm. Impurities in the

amniotic fluid and amniotic bands were not detected in the surveyed women in all groups.

Thus, an ultrasound has revealed the echographic markers of FPI and pathology of the amniotic fluid in patients in the study groups with equal frequency significantly. This and other of the above facts make groups be comparable to each other and allow to objectively identify the best result after three different treatment regimens.

For the purpose monitoring the results of therapy, ultrasound is regularly performed for all women with a frequency of 1 time per week (for the treatment carried out not less than 4 ultrasound investigation each woman). The results are presented in table 2.

Table 2

Structure and frequency of sonographic markers of FPI patients groups researches after of pharmacological correction.

Indicators		Group I, abs. number (%)	Group II, abs. number (%)	Group III, abs. number (%)
Placenta with additional segments	28-30 weeks	1 (2.5)	1 (2.5)	2 (5.0)
	30-32 weeks	__	__	__
	32-34 weeks	__	__	__
	34-36 weeks	__	__	__
Placentomegaly	28-30 weeks	1 (2.5)	__	3 (7.5)
	30-32 weeks	1 (2.5)	__	1 (2.5)
	32-34 weeks	1 (2.5)	__	1 (2.5)
	34-36 weeks	4 (10.0)	__	2 (5.0)
Hypoplasia ofplacental	28-30 weeks	1 (2.5)	__	1 (2.5)
	30-32 weeks	1 (2.5)	__	__
	32-34 weeks	3 (7.5)	1 (2.5)	2 (5.0)
	34-36 weeks	2 (5.0)	1 (2.5)	1 (2.5)
Premature maturation of placenta	28-30 weeks	2 (5.0)	__	4 (10.0)$^{\&}$
	30-32 недель	2 (5.0)	4 (10.0)	3 (7.5)
	32-34 weeks	6 (15.0)	8 (20.0)	7 (17.5)
	34-36 weeks	17 (42.5)	7 (17.5)$^{\#}$	16 (40.0)$^{\&}$
Calcinosis of placental	28-30 weeks	1 (2.5)	1 (2.5)	3 (7.5)
	30-32 weeks	2 (5.0)	1 (2.5)	2 (5.0)
	32-34 weeks	2 (5.0)	3 (7.5)	5 (12.5)
	34-36 weeks	7 (17.5)	5 (12.5)	9 (22.5)$^{\&}$
Expansion of the space intervillous	28-30 weeks	3 (7.5)	__	6 (15.0)$^{\&}$
	30-32 weeks	2 (5.0)	__	4 (10.0)$^{\&}$
	32-34 weeks	9 (22.5)	1 (2.5)$^{\#}$	5 (12.5)$^{\&\mu}$
	34-36 weeks	15 (37.5)	2 (5.0)$^{\#}$	12 (30.0)$^{\&}$

Note: # – the significance of differences of indicators of comparison groups (differences were significant when comparing these two groups $p_{1-2}<0.05$);
& – the significance of the performance differences between the comparison groups (differences were significant when comparing these two groups $p_{2-3}<0.05$);
μ – the significance of differences of indicators of comparison groups (differences were significant when comparing these two groups $p_{1-3}<0.05$).

Against the background of the therapy revealed a positive tendency when assessing the volume and quality of amniotic fluid. In the I group, 10% (4) patients diagnosed with moderately expressed hydramnion amniotic fluid index of 185 ± 25 mm, 22.5% (9) –in the form of moderate oligohydramnios amniotic fluid with an index of 110±10 mm. In group II at 5% (2) women diagnosed with moderately expressed hydramnion amniotic fluid index of 184±20 mm, 20% (8) – in the form of moderate oligohydramnios amniotic fluid with an index of 110±10 mm. In group III 10% (4) of pregnant women revealed moderately severe polyhydramnios amniotic fluid index of 186±23 mm, 25% (10) – in the form of

moderate oligohydramnios amniotic fluid index 111±11 mm. Impurities in the amniotic fluid and amniotic bands were not detected in the surveyed women in all groups.

Analyzing the data obtained after the completion of therapy, it is possible to conclude that there is a positive dynamics in all study groups. However, women who received drug treatment course "Phlebodia 600»® significantly better results for the comparative analysis of sonographic markers FPI before and after therapy. The use of "Phlebodia 600»® is directed to modulation of blood flow and the elimination of stagnation in intervillous space, which increases the compensatory-adaptive mechanisms in the placenta, and therefore increases the amount of amniotic fluid with oligohydramnios.

For the diagnosis of FGRS fetometry obtained data were compared with normative indicators for the duration of pregnancy. When I degrees of severity FGRS – backlog 2 weeks of gestational age the proper under II – within the limits of 3-4 weeks, with the III degree – more than 4 weeks. In the analysis of the degree of severity of FGRS in pregnancy study groups showed no significant differences. I FGRS degree was observed in 72.5% (29) group I patients, 80% (32) group II patients and 75% (30) group III patients. The frequency extent FGRS II had no significant difference in I, II and III and the group diagnosed in 27.5% (11) 20% (8) 25% and (10) pregnant respectively ($p > 0.05$).

After a course of pharmacological correction of positive dynamics of intrauterine condition of the fetus, according ultrasonic fetometry a larger percentage of cases in the II researches group. The results are presented in table 3.

The results suggest a favorable effect of the drug "Phlebodia 600»® on fetal development, which clinically manifested by normalization main indicators of fetus and assess their compliance with the gestational age indices on ultrasound.

Table 3

Comparative analysis the frequency of occurrence degrees of severity of FGRS in pregnant women after treatment between the study groups.

Degrees of severity of FGRS	Group I, (n=40)		Group II, (n=40)		Group III, (n=40)		p
	abs. number	%	abs. number	%	abs. number	%	
FGRS is absent	__	__	22	55.0	4	10.0	$p_{2-3}<0.05$
I degrees	30	75.0	14	35.0	28	70.0	$p_{1-2}<0.05$ $p_{2-3}<0.05$ $p_{1-3}>0.05$
II degrees	10	25.0	4	10.0	8	20.0	$p_{1-2}<0.05$ $p_{2-3}>0.05$ $p_{1-3}>0.05$

Note: p – confidence score difference results between groups I and II, III

When doppler hemodynamic study in the mother-placenta-fetus were carried out a qualitative analysis of the blood flow speeds curves in the following vessels: uterine artery on two sides, umbilical artery and terminal branches, the aorta fetal, middle cerebral artery.

Violations of utero-placental and fetal-placental blood flow was detected in 70,0% (28) women in group I, 75% (30) and 67,5% (27) women's groups II and III, respectively. Violations hemodynamics I A degree (violation of utero-placental blood flow with well-preserved fruit and placental) had no significant differences in the I, II and III groups, and were diagnosed in 62.5% (25) 65.0% (26) 55.0 % (22) of pregnant women, respectively ($p>0.05$). Hemodynamic disturbances I B degree (violation fruit-placental blood flow during a saved uteroplacental) were revealed in the I group, 7.5% (3) women in group II – 10.0% (4) and in group III at the 2.5% (1) women. Violations hemodynamic II degree (simultaneous viola tion of utero-placental and fetal-placental blood flow, does not reach critical values) is diagnosed in only 10% (4) of pregnant women in group III. Hemodynamic disorders III degree (critical violation feto-placental blood flow (or lack of retrograde direction of end-diastolic blood flow), while maintaining or impaired utero-placental blood flow) were not diagnosed in women in researches groups (table. 4).

Table 4

Structure and frequency of hemodynamic disturbances before drug therapy.

The degree of hemodynamic disturbances	Group I (n=40)		Group II (n=40)		Group III (n=40)		p
	abs. number	%	abs. number	%	abs. number	%	
Hemodynamics is not broken	12	30.0	10	25.0	13	32.5	$p_{1-2}>0.05$ $p_{2-3}>0.05$ $p_{1-3}>0.05$
FPI I A degree	25	62.5	26	65.0	22	55.0	$p_{1-2}>0.05$ $p_{2-3}>0.05$ $p_{1-3}>0.05$
FPI I B degree	3	7.5	4	10.0	1	2.5	$p_{1-3}>0.05$
FPI II degree	–	–	–	–	4	10.0	–

Note: p – confidence score difference results between groups I and II, III

Found an increase of resistance index of uterine arteries and fetal umbilical artery, indicating that the decrease in diastolic blood flow and confirms the presence of hemodynamic disturbances. Resistance index of the right and left uterine arteries and fetal umbilical artery did not differ significantly and amounted to 0.67±0.04. 0.65±0.04 and 0.72±0.05 in group I, 0.66±0.04 , 0.6±0.04 and 0.75±0.05 in group II, 0.68±0.04, 0.66±0.04 and 0.71±0.05 in group III, respectively (p>0.05). Resistance index of fetal middle cerebral artery is 0.81±0.06 in the patients in group I, 0.79±0.06 in the patients of group II and 0.80±0.06 in the patients of group III (tab. 6).

The average values systolic- diastolic relationship in the right and left uterine arteries reached 2.71±0.5 and 2.72 ± 0.5 in the group I, 2.66±2.65 and 0.2±0.2 in the group II, 2.74±0.5 and 2.72±0.5 in group III, respectively. The average values systolic- diastolic ratio in umbilical artery did not differ significantly and amounted to 3.6±0.44 in group I, 3.4±0.4 in group II, and 3.6±0.44 in group III (p>0.05). Average index systolic aortic ratio was 8.1 ± 0.4 in group I, 7.8±0.6 in group II, and 7.9 ±0.6 in group III. Average index systolic- diastolic relations in the cerebral artery did not differ significantly and amounted to 5.1±0.9 in group I, 4.8±0.7 in group II, and 4.9±0.8 in group III (p>0.05). Critical blood flow (zero and reversible) in pregnant women in the study groups are not diagnosed (tab. 7).

After completion of treatment showed a significant improvement in hemodynamic parameters utero-placental blood flow and fetus-placental blood flow, which is clinically implemented compensation of placental insufficiency. However, significantly better results were obtained in group II, which is caused by the action of the drug «Phlebodia 600»® (p<0.05).

Significantly more frequently in pregnant women of group II showed no violations of hemodynamics, compared to those groups I and III researches: 87.5% (35 persons), 62.5% (25 persons) and 62.5% (25 persons), respectively (p<0.05). Structure and frequency of hemodynamic disturbances after drug therapy are presented in table 5.

Table 5

Comparative analysis of the frequency of hemodynamic disturbances after drug therapy between the study groups

The degree of hemodynamic disturbances	Group I (n=40)		Group II (n=40)		Group III (n=40)		p
	abs. number	%	abs. number	%	abs. number	%	
Hemodynamics is not broken	25	62.5	35	87.5	25	62.5	$p_{1-2}<0.05$ $p_{2-3}<0.05$ $p_{1-3}>0.05$
FPI I A degree	10	25.0	5	12.5	10	25.0	$p_{1-2}<0.05$ $p_{2-3}<0.05$ $p_{1-3}>0.05$
FPI I B degree	1	2.5	–	–	2	5.0	$p_{1-3}>0.05$
FPI II degree	4	10.0	–	–	3	7.5	$p_{1-3}>0.05$

Note: p – confidence score difference results between groups I and II, III

The decrease of resistance values of the indices of the uterine arteries and arteries of the umbilical cord fetal compared to initial values. Table 6 shows the comparative results of dopplerometria of uterine artery and umbilical artery in pregnant women in the researches group before and after pharmacological correction.

Table 6

Comparative analysis of the dopplerometria data of patients of surveyed groups before treatment and after its completion.

Indicators	Group I, (n=40)		Group II, (n=40)		Group III, (n=40)	
	before treatment, M±m	after treatment, M±m	before treatment, M± m	after treatment, M±m	before treatment, M±m	after treatment, M±m
IR a. uterine dextra	0.67±0.01	0.56±0.02*	0.66±0.01	0.44±0.004$^{*\#}$	0.68±0.01	0.54±0.02$^{*\&}$
IR a. uterine sinistra	0.65±0.01	0.58±0.02	0.64±0.01	0.46±0.004$^{*\#}$	0.66±0.01	0.56±0.02$^{*\&}$
IR a. umbilikalis	0.72±0.04	0.60±0.01*	0.75±0.04	0.56±0.02*	0.71±0.04	0.69±0.01$^{\&\mu}$

Note: # – the significance of differences of indicators of comparison groups (differences were significant when comparing these two groups $p_{1-2}<0.05$);
& – the significance of the performance differences between the comparison groups (differences were significant when comparing these two groups $p_{2-3}<0.05$);
μ – the significance of differences of indicators of comparison groups (differences were significant when comparing these two groups $p_{1-3}<0.05$).

In the comparison group achieved a reduction in resistance indices of the uterine arteries and fetal umbilical artery, compared with baseline values. Resistance index of fetal middle cerebral artery is 0.80±0.06 in pregnant women in group I, 0.75±0.06 in pregnant group II and 0.78±0.06 in pregnant group III. Pulse index of fetal middle cerebral artery after treatment decreased from 2.26±0.17 before 1.86±0.15 in women in group I, with 2.20±0.17 before 1.82±0.14 in women in group II, with a 2.24±0.17 before 1.85±0.15 in women in group III, which was significantly lower compared to before treatment. When comparing the results obtained dopplerometria the middle cerebral artery of fetuses after treatment did not reveal significant differences between the study groups (p>0.05). Therefore, this parameter is not possible to conclude which of the proposed treatment regimens effectively.

The average values systolic-diastolic relationship in the right and left uterine arteries were lower in group II, when compared with I and III and reached 2.36±0.2 and 2.35±0.2 in the group II, 2.68±0.4 and 2.69±0.4 in group I and 2.71±0.5 and 2.70±0.5 and in group III, respectively. Average index systolic-diastolic relations in the umbilical artery was significantly lower in group II, in comparison with the I and III and was 2.6±0.24, 2.98±0.31 and 2.86±0.32 respectively (p<0.05) (tab. 7).

Table 7

The systolic-diastolic relationship dopplerometriavascular of mother and fetus before and after pharmacological correction.

Indicators		SDR in right uterine arteries	SDR in left uterine arterie	SDR in umbilical artery	SDR in aorta of fetal	SDR in middle cerebral artery
I group	before treatment	2.71±0.06	2.72±0.06	3.60±0.09	8.10±0.90	5.10±0.15
	after treatment	2.68±0.04	2.69±0.04	2.98±0.07*	6.80±0.42*	4.91±0.15
II group	before treatment	2.66±0.04	2.65±0.04	3.40±0.08	7.80±0.60	4.80±0.14
	after treatment	2.36±0.03$^{*\#}$	2.35±0.03$^{*\#}$	2.60±0.04$^{*\#}$	5.40±0.18$^{*\#}$	4.40±0.11$^{*\#}$
III group	before treatment	2.74±0.06	2.72±0.06	3.60±0.09	7.90±0.60	4.90±0.15
	after treatment	2.71±0.06$^{\&}$	2.70±0.06$^{\&}$	2.86±0.06*	6.70±0.38$^{*\&}$	4.80±0.14$^{\&}$

Note: * – significance of differences of indicators before and after treatment (the differences were significant in comparison with the original data $p_{b-a}<0.05$);
– the significance of differences of indicators of comparison groups (differences were significant when comparing these two groups $p_{1-2}<0.05$);
& – the significance of the performance differences between the comparison groups (differences were significant when comparing these two groups $p_{2-3}<0.05$);
μ – the significance of differences of indicators of comparison groups (differences were significant when comparing these two groups $p_{1-3}<0.05$).

Use of the drug «Phlebodia 600»® with compensated of FPI and subcompensated stage directed at eliminating venous stasis mainly in the utero-placental complex, improvement of microcirculation, followed by reaction of fetal cardiac activity in the form of increasing its compensatory and adaptive mechanisms.

Fetal status was assessed using antenatal cardiotocography fetus, starting at 30 weeks of pregnancy. At the analysis evaluated of the basal rate, basal rate variability, the presence aktseleratsy and decelerations. Non-stress test (NTS) was considered positive in the case of registration of two or more aktseleratsy amplitude of not less than 15 beats per minute for 40 minutes of observation. Table 8 shows the results before the treatment and after its completion.

Table 8

Comparative analysis of cardiotocography and non-stress test fetuses of patients groups being compared before and after treatment

Indicators CTG	I group (n=40)		II group (n=40)		III group (n=40)	
	before treatment, M±m	after treatment, M±m	before treatment, M±m	after treatment, M±m	before treatment, M±m	after treatment, M±m
The basal rate, beats per minute	127.5±10.09	128.3±10.17	129.3±10.23	142.2±11.25*#	128.2±10.14	130.4±10.87&
The amplitude of the oscillations, beats per minute	7.9±0.63	8.2±0.65	8.2±0.65	10.8±0.85*#	8.1±0.64	8.4±0.78&
The frequency of oscillationin a minute	4.4±0.35	5.6±0.44	4.6±0.36	8.2±0.65*#	4.3±0.34	7.8±0.62*μ
Aktseleratsii, the amount of 60 minutes	2.3±0.18	2.5±0.21	2.4±0.19	4.1±0.32*#	2.2±0.17	2.5±0.21&
Decelerations, the amount of 60 minutes	–	–	–	–	–	–
Total mark, points	7.1±0.56	7.4±0.61	7.3±0.59	9.1±0.72*#	7.2±0.57	7.5±0.61&
Reactive NST	35 (87.5%)	37 (92.5%)	36 (90%)	39 (97.5%)	33 (82.5%)	37 (92.5%)
Areactive NST	5 (12.5%)	3 (7.5%)	4 (10%)	1 (2.5%)*#	7 (17.5%)	3 (7.5%)*&
The propulsion activity of the fetus in 40 minutes	1.8±0.14	2.2±0.17*	1.9±0.15	2.4±0.19*	1.9±0.15	2.3±0.18*
The mean increase in fetal heart rate to a perturbation	13.2±1.04	15.5±1.23	14.6±1.56	18.2±1.36*#	13.8±1.09	16.2±1.28

Note: # – the significance of differences of indicators of comparison groups (differences were significant when comparing these two groups $p_{1-2}<0.05$);
& – the significance of the performance differences between the comparison groups (differences were significant when comparing these two groups $p_{2-3}<0.05$);
μ – the significance of differences of indicators of comparison groups (differences were significant when comparing these two groups $p_{1-3}<0.05$).

According to the CTG fetus comparing groups of patients on the background of hemodynamic utero-placental and fetal-placental blood flow to 100% in a state of chronic intrauterine hypoxia. Total Score CTG below 8 points: in the I group – 7.1±0.56. in II group – 7.3±0.59, in the group III – 7.2±0.57. Low frequency oscillations and the number aktseleratsy: group I – 4.4±0.35 and 2.3±0.18, in II group – 4.6±0.36 and 2.4±0.19, in the group III – 4.3±0.34 and 2.2±0.17 respectively. Availability areactivity NST in 12.5% (5) fruit in group I, 10% (4) fruit in group II and 17.5% (7) fetus in group III. By analyzing the data obtained after the completion of therapy, it is possible to conclude that there is a positive dynamics in all study groups.

The results suggest the positive effect of the drug «Phlebodia 600»® on intrauterine fetal compensatory and increase its abilities to adapt to hypoxia in a larger percentage of cases compared with the preparations «Pentoxifylline»® and «Curantil 25»®.

The term of delivery in pregnant group I was on average 36.8±0.8 weeks in groups II and III – 37.8±0.7 and 37.1±0.8 weeks respectively. In the analysis of child growth and birth weight following peculiarities have been revealed (figure 2, figure 3).

Analysis of the newborn state showed significant differences in the examined groups. The average Apgar score at 1 and 5 minutes in group II was 7.50±0.59 and 8.20±0.65 and was higher compared to groups I and III, where the Apgar score at 1 and 5 minute was 6.76±0.53 and 7.65±0.62; 6.95±0.55 and 7.65±0.62 respectively (tab. 9).

In summary, it can be concluded that the drug «Phlebodia 600»® has a positive effect on the state of the fetus and newborn. A course of treatment has led to the birth of children a greater body weight, significantly less frequently diagnosed pathologies of perinatal period. Due to the fact that the drug of natural origin, it has no side effects on the fetus. The study did not reveal a single case of sensitization newborn or the appearance of long-term complications of drug therapy.

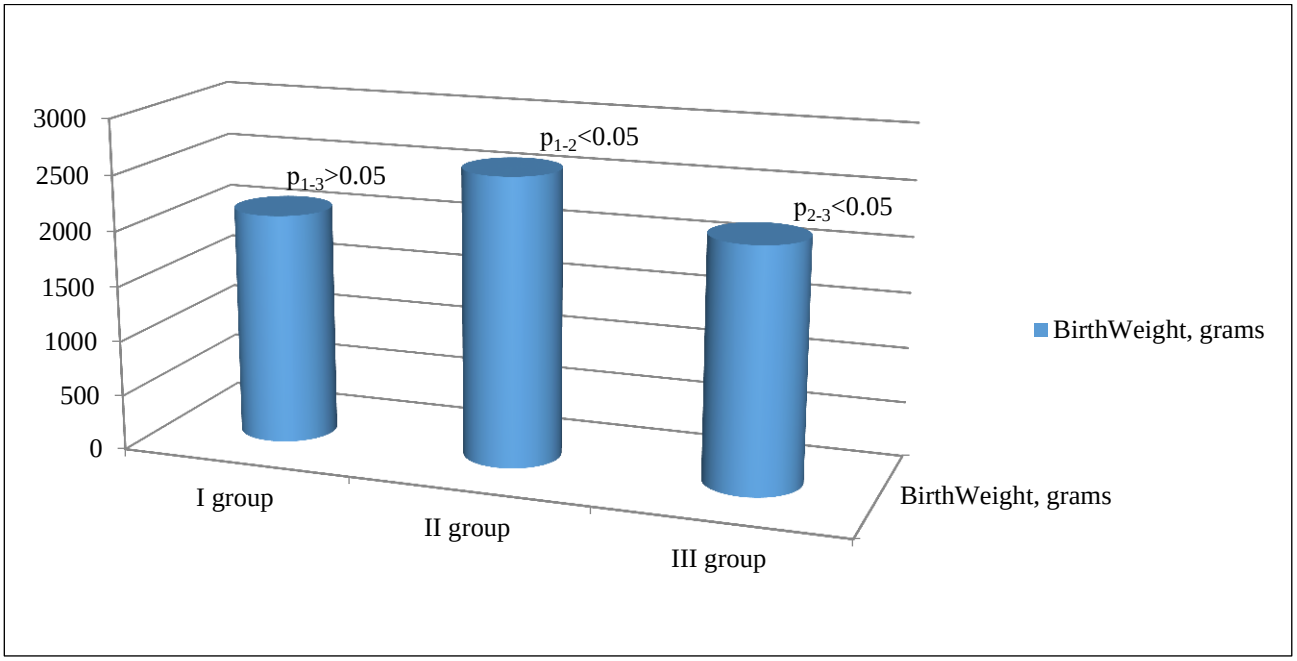

Fig. 2. Birth weight, grams
Note: p<0.05 – confidence score difference results between groups I and II, III

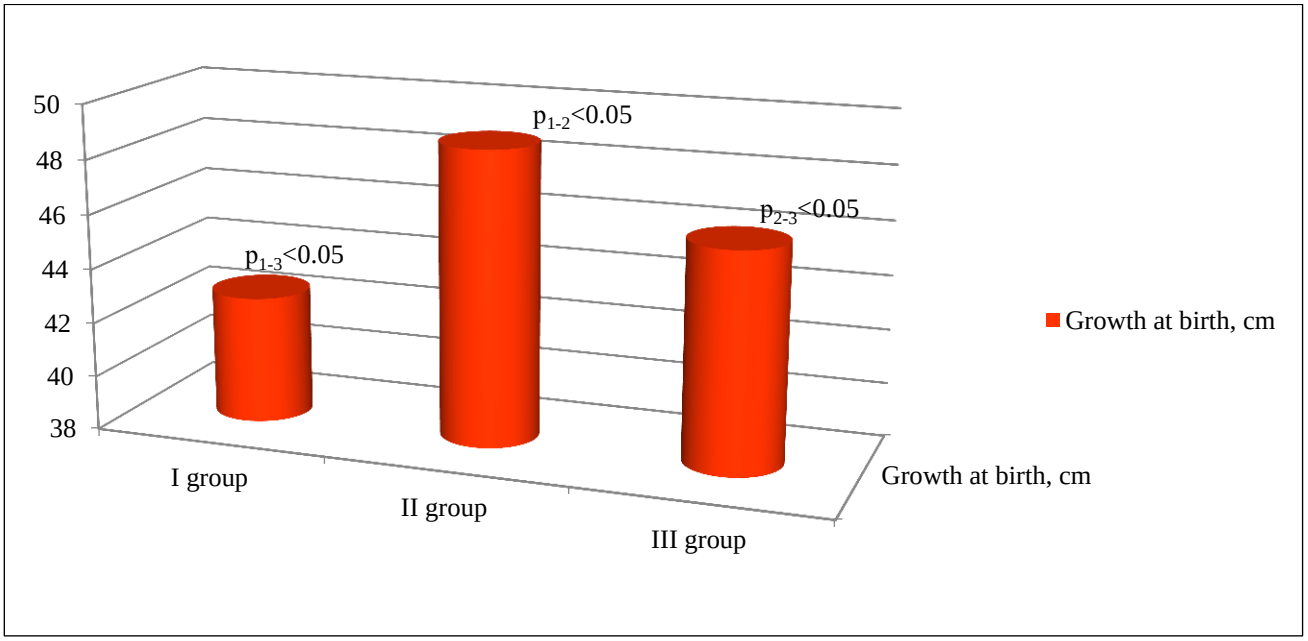

Fig. 3. Growth at birth, cm
Note: p<0.05 – confidence score difference results between groups I and II, III

Table 9

The comparative analysis of the data of the physical development of the child at birth in the studied groups

Indicators	I group (n=40)	II group (n=40)	III group (n=40)	p
	M±m	M±m	M±m	
Head Circumference, cm	29.55±2.50	33.05±2.61	31.80±2.52	$p_{1-2}<0.05$ $p_{2-3}>0.05$ $p_{1-3}>0.05$
Chest circumference, cm	27.15±2.31	31.03±2.45	29.60±2.34	$p_{1-2}<0.05$ $p_{2-3}>0.05$ $p_{1-3}>0.05$
Apgar score at birth and 5 minutes later	6.76±0.53 7.65±0.62	7.50±0.59 8.20±0.65	6.95±0.55 7.65±0.62	$p_{1-2}>0.05$ $p_{2-3}>0.05$ $p_{1-3}>0.05$ $p_{1-2}>0.05$ $p_{2-3}>0.05$ $p_{1-3}>0.05$

Note: p – confidence score difference results between groups I and II, III

On gross examination the average weight of placenta was in I group 447.75±35.42 g, in group II – 497.75±39.38 g, in group III – 467.75±37.01 g (tab. 10). As a result of pathological investigations afterbirths with FPI revealed that it is the basis of histological involution dystrophic and compensatory-adaptive reactions in the placenta, chorionic villus violation of maturation, inflammatory changes in of afterbirth. With changes in the structure of the placenta caused by pathology in the mother's body, strengthened existing compensatory reaction, and there are new, which provides for a certain period of relatively high functional activity, and as a consequence the maintenance of satisfactory fetal life.

Table 10

Pathological examination afterbirth

Histological structure	I group (n=40)	II group (n=40)	III group (n=40)
	abs. number (%)	abs. number (%)	abs. number (%)
Microscopically villi of mature, the umbilical cord and membranes normal histological structure (mature placenta)	9 (22.5)	29 (72.50)#	10 (25.0)&
Involutive-dystrophic changes	26 (65.0)	7 (17.5)#	28 (70.0)&
Compensatory and adaptive change	10 (25.0)	11 (27.50)	13 (32.5)
Inflammatory changes	6 (15.0)	2 (5.0)	4 (10.0)
The average weight of placenta, gram,M±m	447.75±35.42	497.75±39.38	467.75±37.01

Note: # – the significance of differences of indicators of comparison groups (differences were significant when comparing these two groups $p_{1-2}<0.05$);
& – the significance of the performance differences between the comparison groups (differences were significant when comparing these two groups $p_{2-3}<0.05$);
μ – the significance of differences of indicators of comparison groups (differences were significant when comparing these two groups $p_{1-3}<0.05$).

In the study of placentas it was found that the compensatory-adaptive reactions (a measurement of the fetus and placenta adaptation to adverse conditions – in this case placental insufficiency) were present in a greater percentage of cases in group II. Histologically mature placenta (microscopic villi of mature, the umbilical cord and membranes normal histological structure) was significantly more frequent diagnosed in group II, when compared with the other two groups of investigations, patients who failed to achieve compensation of placental insufficiency, and after a pharmacological correction of the results of ultrasound examination was not deviations in fetometry their fetuses ($p<0.05$).

Any treatment suggested by a pregnant woman should be evaluated not only by the effectiveness of prescription drugs, but also to their security for both mother and fetus.

The presence of undesirable effects following the correction of placental insufficiency with delayed development of the fetus syndrome is presented in table 11. Pregnant women who participated in the study, one of the drawbacks of «Curantil 25»® noted time and the multiplicity of reception – the drug should be taken before meals or 1.5-2 hours after the meal three times a day. «Pentoxifylline»® in the hospital introduced slowly into intravenously drip in, after 20% (8) women complained about the presence of painful haematomas in the area of the cubital fossa vein.

The active ingredient in the formulation «Curantil 25»® has a full chemical structure, as well as in the preparation «Pentoxifylline»®. This fact increases the number of side effects and their degree of severity. Cases of hypotension and tachycardia demanded correction using drugs and led to the cancellation of these drugs.

Table 11

Comparative analysis of the incidence of side effects after a drug therapy for patients in investigations groups

Symptoms	I group, person (%)	II group, person (%)	III group, person (%)
Headache	4 (5.0%)	–	6 (15.0%)
Dizziness	10 (25.0%)	–	8 (20.0%)
Nervousness	–	–	1 (2.5%)
Sleepiness or insomnia	–	–	—
Hypotension	8 (20.0%)	–	12 (30.0%)
Heart palpitations	4 (10.0%)	–	5 (12.5%)
Facial a hyperemia	6 (15.0%)	–	5 (12.5%)
Heartburn	2 (5.0%)	–	4 (10.0%)
Nausea	2 (5.0%)	–	2 (5.0%)
Hematoma at the site of injection	8 (20%)	–	–
Assigned course of therapy is carried out fully observing the the appropriate dosing regimen	36 (90.0%)	40 (100%)	28 (70.0%)

When selecting drugs for treating pregnant women also should consider such a thing as «compliance» – consent of the patient to follow the doctor's recommendations. All pregnant women who took part in the study, noted the absence of side effects from taking «Phlebodia 600»® preparation, indicating a good tolerability. This fact has allowed all the women to complete the assigned course, and the multiplicity of reception – 1 times a day, is one of the benefits of the drug and determines the ease of application. The absence in the II group investigations of unwanted side effects can be explained by the fact that the active ingredient in the formulation «Phlebodia 600»® is diosmin – natural bioflavonoid extracted by extraction from plants of the genus Rutaceae. However, a common problem of drugs on the basis of diosmin is a low bioavailability due to poor absorption in the gastrointestinal tract. The implication of this – is gradually coming clinical effect is in direct proportion to the duration of use and the value of a daily dose of diosmin. French company «Laboratory Innotech Internacional» managed to get a semisynthetic diosmin with improved by simultaneous aggregation of the two agents compared to the natural analogue.

Thus, analyzing the fetometric parameters of children at birth and the structure of the incidence of newborns, we can note a significantly better result in the group where the patients took the preparation «Flebodia 600»®. Similar results, which testify to the favorable effect of «Fleobodia 600»® on the fetal development of the fetus, were obtained by L.S. Logutova in 2007 and E.V. Prodanova in 2011 [2, 10]. However, in the course of these studies, this drug

was used as part of complex therapy of fetoplacental insufficiency, which does not allow attributing the obtained clinical effect to the effect of the drug with proven reliability. Whereas in our study, emphasis was placed on monotherapy of fetoplacental insufficiency with fetal development retardation syndrome, and the clinical effects obtained attest to the pharmacodynamic advantage of the preparation «Flebodia 600»®.

Conclusions.

1. From a position of evaluating of compliance preparations «Pentoxifylline»®, «Phlebodia 600»® and «Curantil 25»® includes the pharmacokinetics of the drug, dosage form and the route of administration, dosing frequency, the frequency of adverse effects, conducting a course of therapy in full preparation «Phlebodia 600»® authentically it is an effective and justified ($p<0.05$).

2. After pharmacological correction significantly better results were obtained in group II, which is due to the action of the drug «Phlebodia 600»®, which is equivalent to improve hemodynamics in uterine vessels, and in the umbilical artery of the fetus ($p <0.05$), whereas «Pentoxifylline»® has a partial positive effect on the mother and feto-placental blood flow and «Curantil 25»® mainly affects the uterine blood flow.

3. A course of treatment with «Phlebodia 600»® as compared to the drugs «Pentoxifylline»® and «Curantil 25»® led to the birth of children a greater body weight, significantly less frequently diagnosed pathology of perinatal period ($p<0,05$). During the study did not reveal a single case of sensitization newborn or the appearance of delayed complications of drug therapy.

4. Pathomorphological investigation of afterbirth revealed that histological basis FPI are involutive-degenerative and inflammatory changes, violation of maturation of chorionic villi. Morphologically mature placenta was diagnosed significantly more frequently in group II, 72.5% (29) patients with compensated placental insufficiency on the background of pharmacological correction and the results of ultrasound examination has not been revealed abnormalities in fetometry their fetuses ($p<0.05$).

This work was carried out on the basis of the Department of Obstetrics and Gynecology of the State Public Health Service of the KSMU of the Ministry of Health of the Russian Federation and based on the Oblast Perinatal Center of the city Kursk Klyicheva Olga Igorevna under the guidance of the scientific leaders of Lazareva Galina Anatolevna and Khuraseva Anna Borisovna.

Conflicts of Interest: The authors have no conflict of interest to declare.

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