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PECULIARITIES OF THE FORMATION OF THE FUNCTIONAL SYSTEM "MOTHER-PLACENTA-FETUS" BY THE INFLUENCE OF SMALL DOSES OF RADIATION

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Summary

Introduction. *137Cs ecosystem pollution is a source of radiation for humans. Undifferentiated cells capable of rapid division are the most vulnerable to ionizing radiation. Therefore, the fetoplacental and immune systems should be expected powerful responce to ionizing radiation. The functional capacity of the placenta determines pregnancy scenarios.*

Aim: *to study the features of the formation of the fetoplacental system under the influence of low doses of radiation.*

Materials and methods. *Pregnant women were in two groups, according to the design. The main (1) group included 60 women with reproductive losses in their history and a threat of termination to the current pregnancy, control (2) group consisted of 30 women with a physiological course of pregnancy and an uncomplicated anamnesis. The found incorporation of 137Cs in the placentas of the women of the studied groups was on β-spectrometry. The nature of placental damage was studied using the pathomorphological examination. The expressions of vimentin and CEA were studied in the structures of the placenta using immunohistochemistry. The effects of radiation on the functional system "mother-placenta-fetus" was determined in immunological, hormonal, biochemical, and bacteriological studies.*

The study was approved by the Medical Ethics Commission of the State Institution "Institute of Pediatrics, Obstetrics and Gynecology named after Academician O. M. Lukyanova of the National Academy of Medical Sciences of Ukraine" (Protocol No. 3 of 07.06.2017).

The results were statistically processed on a PC using Microsoft Excel-2016 using Fisher's angular transformation criterion. Differences in comparative values are considered probable if $p < 0.05$ (probability index more than 95%).

The research was carried out as a fragment of the research work of the State Institution "Institute of Pediatrics, Obstetrics and Gynecology named after Academician O.M. Lukyanova of the National Academy of Medical Sciences of Ukraine" "To develop the latest and improve existing technologies for the diagnosis, prevention and treatment of premature abortion in women with miscarriage, taking into account the placenta passport" (2018-2020). Code ВН.20.00.02.18, state registration number 0118U000039, КПКВ 6561040.

Research results. *According to the results, chronic radiation stress plays a decisive role in the multifactorial nature of placental dysfunction and antenatal losses. Activity up to 1.0 Bq/kg of 137Cs does not affect the course of gestation. The compensatory capacity of the placenta remains preserved at the accumulation of 1.1 to 4.4 Bq / kg of 137Cs. It is possible to prolong the pregnancy until term delivery. As a result of exposure to 4.5-10.4 Bq/kg of 137Cs, the stroma of the maternal surface of the placentas is damaged. At the same time, the pregnancy is terminated prematurely, at 28-36 weeks + 6 days, but thanks to the preservation of compensatory reactions in the placenta, the children are born alive. Accumulation in placentas of more than 10.4 Bq/kg of 137Cs is a probable factor in antenatal death of the fetus and early premature birth, as both maternal and fetal structures of the placenta are damaged.*

Conclusions. *Internal irradiation by incorporated 137Cs damages the architecture of the placenta, which complicates the course of gestation. Extreme effects depend on the volumetric activity incorporating 137Cs and compensatory placental properties. The placental accumulation of 4.5 to10.4 Bq / kg of 137Cs triggers premature labor. Accumulation in the placenta of more than 10.4 Bq / kg 137Cs is a probable factor in antenatal fetal death and premature birth. An imbalance of steroid hormones and peroxide hemostasis system are predictors of placental dysfunction and termination of pregnancy. Expression of vimentin is a marker of placental destruction by internal exposure to radionuclides. Expression of CEA is a marker of premature birth and the antenatal death of the fetus.*

Keywords: *Pregnancy; Placenta; Reproductive Losses; 137Cs; Vimentin; CEA.*

Introduction

Defining markers of premature birth is an urgent need for modern obstetrics science. Premature birth is often the result of complex pathophysiological phenomena of uncertain etiology [1-5]. The frequency of premature birth is 75% of all pregnancy losses [3, 5]. Modern diagnostics, pre-pregnancy preparation, pathogenetic treatment, and the latest delivery technologies cannot always prevent fetal loss. Scientists are trying to find the causes of reproductive losses by studying local processes in the placenta [6-13]. The internal irradiation with incorporated radionuclides is a factor that disrupts the architecture of the placenta [6,14]. In this regard, the problems in Chornobyl are interesting from the view of consequences for the "mother-placenta-fetus" functional system. More than 36 years have passed since the accident at the Chornobyl NPP (ChNPP), which no analogs in the world in terms of the variety of radionuclides, the area affected, and the consequences [15, 16]. 137Cs pose the greatest danger

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to the population due to contamination of soil, drinking water, and agricultural products. The power of internal irradiation determines the content of the isotope in the final products of agricultural production. The area of 137Cs radioactive contamination in Ukraine in 1986 was 53.5 thousand km2. In a radius of 300 km from the Chornobyl NPP, 137Cs contamination was the largest and amounted to 1500 kBq / m2. Due to the radioactive decay, the area of agricultural land with 137Cs contamination above 37 kBq / m2 has three decades later halved [16]. However, radioisotope contamination of the ecosystem remains a source of external and internal human exposure. Undifferentiated cells capable of rapid division are the most vulnerable to ionizing radiation. Therefore the fetoplacental and immune systems should be expected powerful respond to ionizing radiation. The functional capacity of the placenta determines pregnancy scenarios.

The work aims to study the features of the formation of the fetoplacental system under the influence of low doses of radiation.

Materials and methods

The pregnant women have carried out examinations in laboratories at the SI “Institute of Pediatrics, Obstetrics, and Gynecology named after Academician Elena M. Lukyanova of the National Academy of Medical Sciences of Ukraine”. All pregnant women are Ukrainian, without chronic somatic pathology. The mean age of women was 33.4 ± 5.2 years. More women (69.4%) live in Kyiv and the region. Respectively, in the western, eastern, and central regions of Ukraine lives, 8.5%, 4.8%, and 17.3% of women. Pregnant women were in two groups, according to the design. The first (1) group included 60 women with reproductive losses in their history and a threat of termination to the current pregnancy, control (2) group - 30 women with a physiological course of pregnancy and an uncomplicated anamnesis. For detailed analysis, subgroups formed within the main group. Subgroup 1a included 38 women who gave birth at 37-40 weeks, despite the complicated course of the current pregnancy, the 1b subgroup - 13 women who gave birth at 28-36 weeks + 6 days, and the 1c subgroup - 9 women who gave at 22-27 weeks + 6 days.

The course of pregnancy largely depends on the health of the reproductive organs on the eve of fertilization. Reproductive anamnesis of pregnant women was studied retrospectively. 60% of women in the first group had disorders menstrual cycle, leiomyoma, ovarian cyst, and endometrial hyperplasia. Hyperandrogenism had the cause of reproductive losses in 12.8% of women and hyperprolactinemia in 37.2% of subjects. Past pregnancy terminated in the first trimester in 76.7% of women in the first group. In 37.2% of women, abortion became habitual (up to 9 episodes in the anamnesis). Almost 20.9% of women gave birth prematurely. In 5 (14.0%) pregnant fetuses antenatal died at 34, 36, and 38 weeks of gestation. The probable cause of reproductive losses in 73.3% of women was a hormonal imbalance, in 30.2% - hereditary thrombophilia, in 53.5% - sexually transmitted infections, and cervical insufficiency in 33.7% of pregnant. Almost 90% of women were diagnosed with several probable causes of abortion. Thus, the stress of the reproductive resources contributed to their exhaustion, which explains the pathological course of each subsequent pregnancy.

Pregnant women had examined for their clinical, immunological, hormonal, biochemical, and bacteriological status. The functional capacity of the fetoplacental complex had assessed by serum progesterone, 17β-estradiol and placental lactogen (PL), estriol excretion, and the ratio of sex hormones in the vaginal environment. Daily excretion of estriol level was determined after 20 weeks of gestation by the method of Ittrich [17]. The pregnancy outcome was predicted with indices of maturation (IM), pyknosis (IP), and eosinophilia (IE) by cytology examination, using the method of H. Shor, modified by M. Arsenyeva [18]. Peroxidic hemostasis and adaptive capacity had assessed by prooxidant, antioxidant, and cortisol levels. Immunological studies were carried out by the immune-enzyme method using the photometer "Multiscan Plus" (Finland), analyzer "Medtronic" (Sweden), and cytofluorimeter "D×Flekh" (USA); the hormonal studies with the analyzer "MSR-1000" (USA); biochemical studies using spectrophotometer "Specol-11" (Germany), and bacteriology by nephelometer "BD Phoenix Spec" (USA).

The found incorporation of 137Cs in the placentas of the women of the studied groups was on β-spectrometry. The volumetric activity of the radionuclide 137Cs was measured using the "Scaler RC-101" analyzer (Japan). The nature of placental damage was studied according to the protocol by morphology examination of the placenta (form No. 013-1/0) [6]. Sections of the placenta 5±1 μm had treated with paraffin, hematoxylin, and eosin or picrofuksin. Structural changes in placentas were detected using Olympus BX51 and Axioskop 40 microscopes. In the placentas were studied the expressions CEA/CD66e Ab-2 (Thermo Scientific; № RB-368-A0) and Vimentin (clone SP20, Thermo Scientific; № RM-9120-SO) using streptavidin peroxidase indirect detection method and imaging system of "UltraVision Quanto HRP DAB" (Thermo Scientific; № TL-015-QHD). The evaluation of Immunohistochemical reaction (IHCR) (in 100 cells in 10 fields of the view at magnification ×400) was the scoring system. The evaluation prevalence of IHCR: 0 points in case of no color, 1 point - less than 10% positively stained cells; 2 points - in case 10-50% stained cells; 3 points - more than 50% stained cells. The evaluation expressiveness of IHCR: 0 points in case of no color, 1 point - weak color; 2 points - a moderate stained; 3 points - an expressive color.

The study was approved by the Medical Ethics Commission of the State Institution "Institute of Pediatrics, Obstetrics and Gynecology named after Academician O. M. Lukyanova of the National Academy of Medical Sciences of Ukraine" (Protocol No. 3 of 07.06.2017).

The results were statistically processed on a PC using the Microsoft Excel-2016 package, using Fisher's angular transformation test. The comparative value differences considered probable if $p < 0.05$ (probability index greater than 95%).

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Results

Metabolism of steroid hormones plays a crucial role in the pathogenesis of reproductive losses [19, 20]. Tables 1 and 2 are the levels of sex hormones during pregnancy in women of the first group. Progesterone deficiency indicates the functional failure of the corpus luteum at the beginning of pregnancy and the placenta after 16 weeks. High estradiol in serum is a marker for miscarriage. Synthesis of 17β-estradiol in the II trimester going at the placenta. The level of the hormone reflects the quality of the uteroplacental circulation. A reduced level of 17β-estradiol in the blood of pregnant women of the first group is a marker of placental dysfunction.

Determination of the ratio of sex hormones in the vaginal environment allows for predicting the course of pregnancy in advance (table 3). Progestogenic smears are characteristic of physiological pregnancy, and estrogenic or atrophic smears for premature termination of pregnancy. The high number of surface cells and increased index of cariopyknosis (IC) and index of eosinophilia (IE) in the vaginal environment of pregnant women of the main group indicates progesterone deficiency starting from the I trimester. Estrogen smears prevailed in women of the main group. The parabasal cells in smears of the first group indicate distress in the fetus. Colpocytological smears in every third woman had signs of inflammation.

Table 1

The concentration of progesterone in the serum of pregnant in the dynamics of pregnancy, M ± m, nmol / l

Groups	n	The concentration of progesterone in the blood		
		before 12 weeks	13−24 weeks	25−36 weeks
Main group	30	57,5 ± 5,03 *	93,4 ± 4,9 *	157,5 ± 11,7 *
Control group	30	84,6 ± 8,9	139,1 ± 5,7	283,8 ± 9,3

Note:* the probability of difference with control, p < 0,01.

Table 2

The concentration of estradiol in the serum of pregnant in the dynamics of pregnancy, M ± m, nmol / l

Groups	n	The concentration of estradiol in the blood		
		before 12 weeks	13−24 weeks	25−36 weeks
Main group	30	39,2 ± 2,04 *	28,7 ± 2,1 *	35,6 ± 3,9 *
Control group	30	22,2 ± 1,9	36,9 ± 3,8	56,9 ± 9,4

Note:* the probability of difference with control, p < 0,01.

Table 3

Indicators of colpocytological research in surveyed in the dynamics of pregnancy, M ± m, %

Gestation period	Groups & subgroups		n	Maturation index (cells)			IC	IE
				parabasal	intermediate	superficial		
before 12 weeks	Control group		20	0	81,4 7,6	18,6 ± 2,9	15,0 ± 4,1	10,7 ± 3,1
	Main group & subgroups	1-A	30	0,018 ± 0,017	59,0 ± 4,9 *	40,98 ± 4,9 *	36,5 ± 5,1*	38,7 ± 5,0 *
		1-B	20	0,018 ± 0,017	58,5 ± 6,0 *	41,4 ± 6,0 *	37,7 ± 6,2 *	37,4 ± 5,9 *
		1-C	20	0,05 ± 0,02 *	59,96 ± 2,9 *	39,98 ± 2,9 *	35,6 ± 2,9 *	37,1 ± 2,9 *
13−24 weeks	Control group		20	0	88,8 ± 4,7	11,2 ± 2,2	8,9 ± 2,0	6,1 ± 1,3
	Main group & subgroups	1-A	30	0,16 ± 0,04 *	67,2 ± 2,2 *	32,6 ± 2,2 *	28,3 ± 2,2 *	30,5 ± 2,2 *
		1-B	20	0,06 ± 0,03 *	66,5± 3,0 *	33,4± 3,0 *	29,4 ± 2,8 *	30,9 ± 3,0 *
		1-C	20	0,07 ± 0,03 *	59,3 ± 3,6 *	40,6 ± 3,6 *	36,3 ± 3,7 *	38,4 ± 3,7 *
25−36 weeks	Control group		20	0	90,9 ± 5,0	9,0 ± 0,36	7,9 ± 0,23	5,6 ± 0,3
	Main group & subgroups	1-A	30	0,2 ± 0,07 *	77,7 ± 3,1 *	21,98± 3,1*	21,7 ± 1,8 *	18,5 ± 3,1 *
		1-B	20	0,37 ± 0,06 *	69,3 ± 2,9 *	30,4 ± 2,9 *	26,4 ± 2,8 *	29,3 ± 3,1 *
25−28 weeks		1-C	20	0,98 ± 0,06 *	61,4± 3,1 *	37,6 ± 3,1*	39,7 ± 1,8 *	41,8 ± 3,1 *

Note:* *the probability of difference with control, p < 0,05.*

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The excretion of estriol is a criterion for assessing the fetus. The endocrine glands of the fetus secrete dehydroepiandrosterone, converted into estriol by syncytium. During normal pregnancy increases the daily excretion of estriol. Excretion of the hormone decreases long before clinical manifestations of fetal distress. Compared with controls, pregnant women of subgroups 1b and 1c had a low concentration of estriol in urine, which is associated with fetal distress (table 4).

Table 4

The concentration of estriol in the urine of pregnant in the dynamics of gestation, M ± m, μmol / d

Groups & subgroups		n	The concentration of estriol in the urine			
			20-28 weeks	29-32 weeks	33-36 weeks	37-40 weeks
Main group & subgroups	1a	30	28,1 ± 2,1	35,9 ± 3,8	46,1 ± 7,6	67,0 ± 7,9
	1b	20	24,6 ± 2,6	23,95 ± 2,2 * **	40,0 ± 4,8 *	-
	1c	15	22,8 ± 2,7	-	-	-
Control group		30	27,0 ± 2,9	39,2 ± 5,2	56,4 ± 6,7	79,6 ± 8,7

Note: the probability of difference with control, p < 0,05.*
***:the probability of a difference with 1a subgroup, p < 0,05.*

Determining the content of placental lactogen (PL) in the blood allows for early diagnosis of placental insufficiency. PL deficiency characterizes a pathological condition in which the transport function of the placenta is disturbed, namely the provision of the fetus with the necessary nutrients and oxygen. In the presence of PI, the concentration of PL decreases by 50%, and in the case of fetal distress - almost three times. Such a deviation from the norm threatens the development delay or death of the fetus. Information on the concentration of PL in the serum in pregnant in the dynamics of gestation is in table 5.

Table 5

The concentration of PL in the serum of pregnant in the dynamics of pregnancy, M ± m, nmol / l

Groups & subgroups		n	The concentration of PL in the blood		
			20-24 weeks	25-28-36 weeks	37-40 weeks
Main group & subgroups	1a	30	67,0 ± 7,9 *	144,9 ± 15,8	255,0 ± 18,2
	1в	20	35,9 ± 8,8 * **	73,8 ± 2,2 * **	-
	1c	15	30,6 ± 7,4 * **	60,9 ± 7,8 * **#	-
Control group		30	109,7 ± 11,9	204,5 ± 45,2	279,0 ± 28,6

Note:the probability of difference with control, p < 0,05.*
***the probability of a difference with 1a subgroup, p < 0,05.*
#the probability of a difference with 1b subgroup, p < 0,05.

Information on the concentration of stress-associated hormone cortisol in the biological environments of pregnant women in the first trimester is present in table 6. High cortisol in the blood and urine of pregnant women of the first group indicates glucocorticoid activity of the adrenal and the tension of adaptation mechanisms.

Table 6

Cortisol level in biological environments of subjects in the 1st trimester of pregnancy, M ± m

Groups	n	The level of cortisol	
		in blood, nmol / l	in daily urine, nmol / d
Main group	60	345,8 ± 6,1 *	283,7 ± 2,7 *
Control group	30	284,4 ± 4,3	136,4 ± 9,04

Note:the probability of difference with control, p < 0,05.*

Pregnancy is a new state of immune homeostasis [21, 22]. Immunological suppression is a key to the physiological course of gestation. The T-lymphocytes, B-lymphocytes, and natural killer (NK) cells provide recognition of foreign antigens and timely reaction. Immunocompetent cells differ in phenotype (presence of CD markers) and functions. The common T-cells marker is CD3-complex. According to the CD4 or CD8 CD4+ T-lymphocytes phenotype, T-helpers and T-suppressors are distinguished. CD4+ T-lymphocytes are immune memory cells that perform regulatory functions due to the production of cytokines. CD8+ make up 30% of lymphocytes circulating in the blood, which control cellular immunity. B-lymphocytes, which make up 20% of circulating blood lymphocytes, are responsible for humoral immunity. Natural killers control the early phase of infection by secreting pro-inflammatory cytokines. Membrane molecule CD56 is an exclusive marker of NK cytotoxicity. Most often, NKs presented by CD3-CD56+. The immune indicators in pregnant during gestation shows in table 7.

In the blood of pregnant of the main group, the

relative number of lymphocytes did not differ from the control indicator. However, the absolute number of lymphocytes in the blood exceeded the control indicator during I and II trimesters, $p < 0,05$. The relative amount of CD3+ in the blood of pregnant women of the first group did not differ from the control group. However, the absolute number of CD3+ in the blood of pregnant women increased during gestation. In the blood of pregnant of the main group in the I trimester was found the reduction of CD4+. However, the content CD4+ in the II trimester did not differ from the control indicator. The relative number of CD8+ in the blood of women from the main group differed from the control indicators only in the II trimester. However, the absolute number of CD8+ exceeded the control indicators, starting in I trimester, $p < 0,05$.

The number of CD16+ NK in the blood of patients of the main group in the dynamics of pregnancy is higher than the similar indicators of the control group, $p < 0,05$. CD16+ is responsible for NK cytotoxicity [9]. Physiological pregnancy is typical of a reduction of CD16+ in the blood. A high number of CD16+ and CD3-CD16/56+ in the blood of pregnant of the main group indicates an unfavorable immunobiological symbiosis between the mother and fetus.

Table 7

The immune indicators in examinated pregnant at the dynamics of gestation, M ± m, abs. n., %

Indicators	I trimester		II trimester	
	Main group n=18	Control group n=13	Main group n=18	Control group n=12
Leukocytes	7,4 ± 0,3 *	6,0 ± 0,1	9,0 ± 0,4 *	5,9 ± 0,2
Lymphocytes	24,0 ± 3,8	19,0 ± 2,4	22,5 ± 4,9	21,0 ± 4,1
× 10^9 / l	1,8 ± 0,1 *	1,1 ± 0,1	2,0 ± 0,1 *	1,2 ± 0,1
CD 3+, %	70,0 ± 1,0	70,1 ± 2,1	70,1 ± 2,9	71,9 ± 2,3
× 10^9/л	1,2 ± 0,02 *	0,8 ± 0,02	1,4 ± 0,06 *	0,9 ± 0,01
CD 4+, %	37,1 ± 0,6 *	44,4 ± 2,2	45,2 ± 7,6	50,0 ± 2,1
× 10^9 / l	0,6 ± 0,01	0,5 ± 0,02	0,9 ± 0,2	0,6 ± 0,02
CD 8+, %	26,7 ± 0,7	25,4 ± 1,2	27,6 ± 0,9 *	24,4 ± 0,9
× 10^9 / l	0,5 ± 0,01 *	0,3 ± 0,01	0,6 ± 0,02 *	0,3 ± 0,01
CD4:CD8	1,4 ± 0,1	1,7 ± 0,2	1,8 ± 0,9	2,0 ± 0,3
CD 16+, %	12,5 ± 1,8 *	7,1 ± 1,5	10,8 ± 0,6 *	6,8 ± 0,2
× 10^9 / l	0,2 ± 0,01 *	0,1 ± 0,01	0,2 ± 0,01*	0,1 ± 0,01
CD3-CD16/56+, %	19,4 ± 4,3 *	12,8 ± 2,4	12,2 ± 3,7	10,3 ± 3,4
×10^9 / l	0,25 ± 0,08 *	0,15 ± 0,06	0,18 ± 0,05	0,14 ± 0,08
CD 19+, %	8,2 ± 0,6	7,3 ± 0,8	7,4 ± 0,6	7,4 ± 0,5
× 10^9 / l	0,1 ± 0,01	0,1 ± 0,01	0,1 ± 0,01	0,1 ± 0,01
CIC with medium molecular weight, ODU	16,5 ± 2,3	14,2 ± 3,6	13,5 ± 4,3	16,7 ± 5,6
CIC with low molecular weight, ODU	59,4 ± 6,5	48,6 ± 5,6	49,6 ± 7,7	54,6 ± 6,1
CD 19+, %	8,2 ± 0,6	7,3 ± 0,8	7,4 ± 0,6	7,4 ± 0,5
× 10^9 / L	0,1 ± 0,01	0,1 ± 0,01	0,1 ± 0,01	0,1 ± 0,01
CIC with medium molecular weight, ODU	16,5 ± 2,3	14,2 ± 3,6	13,5 ± 4,3	16,7 ± 5,6
CIC with low molecular weight, ODU	59,4 ± 6,5	48,6 ± 5,6	49,6 ± 7,7	54,6 ± 6,1

Note:*the probability of difference with control, p < 0,05.*

Inflammatory diseases of the genital are a predictor of reproductive losses [23, 24]. Diagnostics confirmed the prevalence of sexually transmitted infections (STIs) among the examined. Thus, almost 20.0% of patients in the main group were diagnosed with STIs during pregnancy. Pregnant women in the control group suffered from STIs three times less often. In 33.4% of pregnant women in the control group, Staphylococcus epidermidis with Candida was detected by bacterial examination. Almost 63.4% of the pregnant women in the main group have found Staphylococcus epidermidis and Intestinal infection. Lack of lactobacilli in pregnant women led to a shift in the pH of the vaginal environment to the alkaline side. Lack of lactobacilli in the vaginal environment increases the risk of infection of amniotic membranes and premature termination of pregnancy.

Most often, in women of the main group, pregnancy was complicated by placental dysfunction (PD). At the heart of PD is an imbalance of oxidation processes and blood supply against the background of a violation of the placental structure and immune homeostasis. Hence, there is interest in studying the morphological component of PD formed under the influence of internal irradiation.

The radioisotope measurement established the accumulation of 137Cs in the placentas of the control group did not exceed 1.0 Bq / kg. At the same time, structural changes in the placenta at 39−40 weeks of pregnancy were natural. The average weight of the

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placentas ranged from 550.0 ± 35.5 g.

Damage to the structure of proteins threatens the vital functions of cells. Vimentin is an intermediate filament of mesenchymal origin, the main protein that controls shape, flexibility, integrity, cell interaction under mechanical stress, and the transport of low-density lipoproteins. In response to cellular stress, vimentin promotes the formation of aggresomes that perform a cytoprotective function. The placentas of the control group have high expressiveness vimentin.

Cancer-embryonic antigen (CEA) is formed in the digestive system of the fetus and is responsible for cell division. After the birth of a child, the synthesis of antigen stops. It is known from the scientific literature that CEA expression is usually not detected in the placenta. As a result of the study found, the control group of placentas did not have CEA.

In placentas of the 1a subgroup, about 1.1−4.4 Bq / kg ^{137}Cs accumulated by radioisotope measurement. Placentas with oval shape. The weight of the placentas ranged from 450.0-610.0 g. The surface placenta on the side of the fetus is smooth. The amniotic membrane is grayish-blue and thin. The umbilical cord is not longer than 55 cm and not wider than 1.5−1.7 cm^2. The umbilical cord slightly thickened due to edema. Blood supply to the maternal surface of the placenta occurs evenly. But, in 30% of cases, the areas of ischemic infarction are determined on the maternal surface of the placentas. The decidual membrane (DM) shows edema, inflammation, hemorrhages, and "afunctional zones" in 50% of cases. The intervillous space (IVS) contains single areas of hemorrhage and increased amounts of fibrin. The villous chorion (VC) is proportionally branched; the density of the villi is appropriate. At the same time, the villi seem to be "walled up" with fibrin, which significantly reduces the area of the syncytial lining of the villi and partially reduces the perfusion of maternal vessels. This condition threatens villous chorion infarction and, ultimately, premature termination of pregnancy.

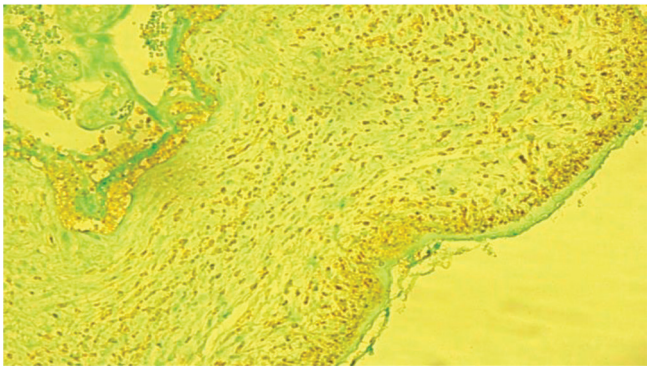

Fig. 1. The placenta. 1b subgroup. Activity 4.5−10.4 Bq / kg 137Cs. Expression of CEA in ChM. Zoom ×100.

The placentas of the 1a subgroup have high expressiveness vimentin. As a result of the study found, the 1a subgroup of placentas did not have CEA.

Subgroup 1b included placentas of women who gave birth to live children at 28−36 weeks + 6 days of gestation. Placentas had significant structural changes due to the accumulation of 4.5−10.4 Bq / kg ^{137}Cs. The placentas are usually oval with an average weight of 480.0 g; the umbilical cord with varicose veins. The ischemia, decidual membrane detachment, hemorrhages, plethora, calcifications, and "afunctional zones" was found on the maternal surface of the placentas. "Afunctional zones" are convergent intermediate (IV) and terminal (TV) villi with stroma fibrosis. Amniotic membranes in 80% of samples are thin, with hemorrhage and inflammatory infiltration. These disorders are named injuries "maternal stromal" of the placenta [10-13].

In the stroma of villus of the 1b subgroup was found moderate (2 points) expression of vimentin. In the decidual (DM) and chorionic membranes (ChM) of the 1b subgroup was found high expression of CEA (Fig.1). In the syncytia of the villus and endothelium of fetal vessels were found single of CEA.

Subgroup 1c included placentas of women who gave birth to stillbirths at 22−27 weeks + 6 days of gestation. The placentas 1c subgroup accumulated 10.5−38.0 Bq / kg 137Cs. In placentas of the 1c subgroup were found acute inflammation and total detachment of the decidual membrane, depletion of compensatory reactions in the intermediate and terminal villi against the background of the global decline in vascular perfusion. Therefore, internal exposure to 137Cs incorporated in the placenta with an activity of more than 10.4 Bq / kg is fatal to the fetus.

A moderate (2 points) expression of vimentin has been in the stroma of villi and endothelium fetus vessels of the 1c subgroup. The high activity of CEA has been in decidual and chorionic membranes, syncytia of villi, and endothelium fetus vessels of the 1c subgroup (Fig. 2).

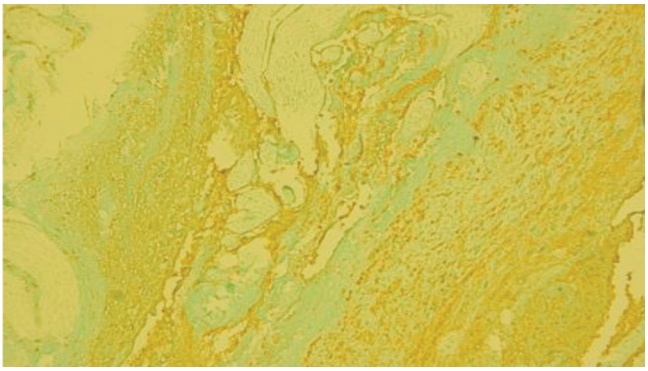

Fig. 2. The placenta. 1c subgroup. Activity 10.5−38.0 Bq / kg 137Cs. Expression of CEA in FM. Zoom ×50.

The functionality of cell membranes is directly related to lipid peroxidation (LPO). Peroxide hemostasis, namely the balance of concentrations of prooxidant and antioxidant components, is an essential condition for life [25, 26]. High levels in the blood of pregnant of the main group in the 1st trimester of diene conjugates (DC), lipid hydroperoxides, malondialdehyde (MDA), and anionic-radical oxygen indicate an imbalance system of antioxidant protection (AP) (Table 8, 9). Depletion of AP leads to the formation of placental insufficiency (PI) and premature termination of pregnancy.

Discussion

The harmonious functioning of the "mother-placenta-fetus" system ensures the physiological

course of gestation. At the same time, an important role belongs to sex steroid hormones [19, 20, 27]. The course of pregnancy in the first trimester depends on the functional ability of the corpus luteum to synthesize progesterone. Endogenous progesterone provides the mechanisms of complete trophoblast invasion: secretory transformation and decidualization of the endometrium, suppression of prostaglandin synthesis and expression of oxytocin receptors, inhibition of calcium transport to myometrial smooth cells, synthesis of progesterone-inducing blocking factor. The high level of estradiol and reduced progesterone in the blood of pregnant of the main group in the I trimester are markers of miscarriage. A reduced level of 17β-estradiol and progesterone in the blood of pregnant women of the main group in the II and III trimesters are markers of placental dysfunction.

The materialization of immunological changes depends on the dominant etiological factor of reproductive losses and maintaining the balance of immune relationships of the "mother-placenta-fetus" system.

Infection against the background of immunosuppression and placental dysfunction leads to fetal distress, premature

Table 8

Indicators of lipid peroxidation in the blood of surveyed women in the dynamics of pregnancy, M ± m

Groups	n	Trimester of pregnancy	Diene conjugates, um. od / ml	Lipid hydroperoxides, μmol / ml	Malonic dialdehyde, μmol / ml	O, OH, H_2O_2
Main group	30	I	62,8 ± 4,1*	2,13 ± 0,06*	149,6 ± 3,8	63,8 ± 3,6*
		II	34,8 ± 3,2	2,12 ± 0,07	144,4 ± 2,6*	54,3 ± 4,3*
		III	46,8 ± 2,1*	3,34 ± 1,1*	152,2 ± 3,1	58,6 ± 2,5*
Control group	30	I	27,9 ± 1,2	1,67 ± 0,04	128,4 ± 3,7	35,3 ± 2,8
		II	29,5 ± 1,2	1,77 ± 0,06	136,4 ± 2,9	36,4 ± 1,7
		III	31,1 ± 2,9	1,99 ± 0,14	142,6 ± 3,6	38,7 ± 1,9

Note:*the probability of difference with control, p < 0,01.*

Table 9

Indicators of antioxidant protection in the blood of surveyed women in the dynamics of pregnancy, M ± m

Groups	n	Trimester of pregnancy	Catalase, μmol H_2O_2 ml	Superoxide dismutase (SOD), um. od. act. / ml / min	Antioxidant activity (AOA), um. od. act. / ml / min	Glutathione peroxidase, μmol / ml	Reduced glutathione, μmol / ml
Main group	30	I	25,7 ± 1,5*	47,8 ± 2,7	1,37 ± 0,03*	2,16 ± 0,04*	2,78 ± 0,02*
		II	38,6 ± 2,4	52,3 ± 2,8	1,34 ±0,05*	3,02 ± 0,06*	3,34 ± 0,06*
		III	32,5 ± 2,1*	49,8 ± 2,3*	1,28 ± 0,03*	2,26 ± 0,04*	3,02 ± 0,04*
Control group	30	I	38,5 ± 2,2	54,8 ± 3,6	1,77± 0,03	2,59 ± 0,02	3,58 ± 0,03
		II	40,6 ± 1,8	61,2 ± 1,4	1,67 ± 0,02	2,53 ± 0,04	3,62 ± 0,02
		III	44,8 ± 1,9	62,4 ± 2,6	1,62 ± 0,03	2,58 ± 0,02	3,74 ± 0,03

Note:** the probability of difference with control, p < 0,01.*

rupture of amnion, and reproductive losses.

The placentas of the main group had a disturbed structure. Naturally, structural changes in the placenta affect its functional capabilities. The morphological substrate of chronic placental dysfunction in the samples of the main group consists of narrowing and tortuosity of spiral arteries, stasis, aggregation or adhesion of formed blood elements, an increase in the amount of fibrin in the intervillous space, calcifications, edema, and fibrosis of the stroma of villus. As a result of a decrease in the volume and area of intermediate and terminal villus, the presence of "afunctional zones" and endothelial dysfunction intraplacental oxygenation and blood circulation in the umbilical cord arteries are disturbed, and fetal distress occurs. A low level of placental lactogen (PL) in the blood and a decrease in estriol excretion in pregnant women of the main group confirms the presence of placental dysfunction and distress in the fetus.

Radiation stress caused by internal irradiation hurts the course of gestation. The incorporation of 137Cs into the placenta disrupts its architecture. Extreme effects differ depending on the volumetric activity of the incorporated agent. In the control placentas, an accumulation of up to 1.0 Bq / kg of 137Cs was detected, which did not affect the course of pregnancy.

The activity of incorporated 137Cs in the placenta of women of subgroup 1a was 1.1 - 4.4 Bq / kg. 30% of placentas had circulatory disorders. Almost 50% of placentas had dystrophic changes. At the same time, in the placenta were preserved compensatory capabilities. In this regard, with the timely appointment of pathogenetic therapy, it is possible to prolong the pregnancy to 37-40 weeks.

The activity of incorporated 137Cs in the placenta of women of subgroup 1b was 4.5 - 10.4 Bq / kg. The damaged

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the maternal surfaces of placentas subgroup 1b by internal irradiation. The changes belong to the category of maternal stroma damage. As a result, the dystrophic changes caused by primary vascular disorders are inhibited intraplacental oxygenation and oxygen transport from the intervillous space to the vessels of the umbilical cord. At the same time, the fetus develops distress. Insufficient intraplacental oxygenation, synthesis of low-molecular-weight mediators of inflammation, and activation of phagocytosis are triggers of structural changes in the cervix, rupture of the fetal membranes, and premature labor. In women of the 1b subgroup, the pregnancy ended prematurely, at 28-36 weeks + 6 days, but their children were born alive, thanks to the preservation of compensatory reactions in the placenta. Usually, the expression of CEA does not detect in the placenta. However, the placentas of the 1b subgroups observed a high expression of CEA.

Chronic radiation stress caused by the accumulation in the placenta of more than 10.4 Bq / kg of 137Cs (1c subgroup) led to the development of systemic endothelial dysfunction, activation of the pro-inflammatory response, and the formation of pro coagulation potential. Subgroup 1c damaged both maternal and fetal structures of the placentas. Depletion of compensatory reactions in samples of the 1c subgroup was due to acute inflammation of the decidual membrane, immaturity of intermediate and terminal villi, and a global decrease in fetal vascular perfusion against the background of the total detachment of the placenta. Decompensation of the adaptive mechanisms of the "mother-placenta-fetus" system is the cause of antenatal fetal death. At the same time, the placentas of the 1b subgroups observed a high expression of CEA.

The morpho-functional state of cell membranes is directly related to LPO processes [26]. The authors proved that ionizing radiation affects metabolism, enzymatic processes, and the permeability of cell membranes [14-16]. Defects of POL and AP found in women of the main group lead to the accumulation of overactive CO2 products, which threatens the vital activity of cells, and activates the arachidonic cascade, synthesis of prostaglandins, and premature labor. As a result of overexpression of toxic aggregates, the risk of tissue destruction is due to the formation of large amounts of insoluble, partially denatured, or mutant proteins. The main structural protein of cells, vimentin, rushes to the rescue. Vimentin promotes the formation of aggresomes that perform a cytoprotective function. However, vimentin in the placentas of the 1c subgroups is insufficient activity. As a result of structural changes, in placenta disrupted metabolism, transport of nutrients, and gas exchange. In this case, the culmination is antenatal fetal death.

Thus, chronic radiation stress plays a critical role in the multifactorial nature of placental dysfunction and antenatal losses, involving hormonal, immunological, bacterial, and hypercoagulable disorders [21].

Conclusions

Internal irradiation by incorporated 137Cs disrupts the architecture of the placenta, which complicates the course of gestation. Extreme effects depend on the volumetric activity of the incorporated 137Cs and compensatory placental properties. The placentas accumulation of 4.5 to10.4 Bq / kg of 137Cs triggers premature labor. Accumulation in the placenta of more than 10.4 Bq / kg 137Cs is a probable factor in antenatal fetal death and premature termination of pregnancy. An imbalance of steroid hormones and peroxide hemostasis system are predictors of placental dysfunction and termination of pregnancy. Expression vimentin is a marker of placental destruction by internal exposure to radionuclides. Expression CEA is a marker of premature birth and antenatal death of fetus.

Prospects for further research are aimed at preventing reproductive losses and pathological conditions caused by internal exposure.

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ОСОБЛИВОСТІ ФОРМУВАННЯ ФУНКЦІОНАЛЬНОЇ СИСТЕМИ «МАТИ-ПЛАЦЕНТА-ПЛІД» ПІД ВПЛИВОМ МАЛИХ ДОЗ РАДІАЦІЇ

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Резюме

Вступ. Забруднення екосистеми ^{137}Cs – джерело радіації в людини. Найбільш уразливі до іонізуючого випромінювання - недиференційовані клітини, які здатні до швидкого поділу. Звідси, саме від фето-плацентарної та імунної систем слід очікувати потужну реакцію на дію іонізуючого випромінювання. Функціональність плаценти визначає сценарії вагітності.

Мета дослідження. Встановити особливості формування фето-плацентарної системи в умовах впливу малих доз радіації.

Матеріали і методи дослідження. Вагітні були розділені на групи, згідно з дизайном дослідження: до основної (1) увійшли 60 жінок з репродуктивними втратами в анамнезі та ознаками передчасного переривання поточної вагітності, до контрольної (2) - 30 осіб з фізіологічною вагітністю та неускладненим анамнезом. Накопичення в плаценті 137Cs встановили шляхом β-спектрометрії. Характер ушкоджень визначали за допомогою патоморфологічного дослідження плацент. В плацентах методом імуногістохімії вивчали експресію віментину і РЕА. Вплив радіації на функціональну систему «мати-плацента-плід» оцінювали за результатами імунологічних, гормональних, біохімічних та бактеріологічних досліджень.

Дослідження затверджені Комісією з медичної етики ДУ «Інститут педіатрії, акушерства і гінекології імені академіка О. М. Лук'янової НАМН України» (протокол № 3 від 07.06.2017).

Результати обробляли статистично на ПК за допомогою пакета Microsoft Excel-2016, використовуючи критерій кутової трансформації Фішера. Відмінності порівняльних значень вважаються ймовірними, якщо $p < 0,05$ (індекс вірогідності більше 95%).

Дослідження виконані у межах науково-дослідної роботи ДУ «Інститут педіатрії, акушерства і гінекології імені академіка О. М. Лук'янової НАМН України» «Розробити новітні та вдосконалити існуючі технології діагностики, профілактики та лікування передчасного переривання вагітності у жінок з невиношуванням з урахуванням паспорта плаценти» (2018-2020 рр.). Шифр ВН.20.00.02.18, № держреєстрації 0118U000039, КПКВ 6561040.

Результати дослідження. Довели, що хронічний радіаційний стрес відіграє визначну роль у багатофакторній природі плацентарної дисфункції та антенатальних втрат. Встановили, що активність ^{137}Cs до 1,0 Бк/кг не впливає на перебіг гестації. Компенсаторна здатність плаценти зберігається при інкорпоруванні 1,1 - 4,4 Бк/кг ^{137}Cs. Можливо зберегти вагітність до терміну пологів. В результаті внутрішнього опромінення 4,5-10,4 Бк/кг ^{137}Cs ушкодження зазнає строма материнської поверхні плацент. При цьому вагітність переривається передчасно - у 28-36 тижнів + 6 днів. Але діти народжуються живими завдяки збереженню компенсаторних реакцій у плаценті. Накопичення понад 10,4 Бк/кг ^{137}Cs - ймовірний чинник антенатальної загибелі плоду та

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ранніх передчасних пологів, оскільки ушкоджень зазнають як материнська, так і плодова структура плацент.

Висновки. Внутрішнє опромінення 137Cs порушує архітектоніку плаценти, що ускладнює перебіг вагітності. Екстремальні ефекти залежать від об'ємної активності включеного ^{137}Cs та компенсаторної спроможності плаценти. Дисбаланс стероїдних гормонів та системи перекисного гемостазу - провісники плацентарної дисфункції та невиношування вагітності. Експресія віментину - маркер плацентарної деструкції при внутрішньому впливі радіонуклідів. Експресія РЕА в плаценті - маркер передчасних пологів та антенатальної загибелі плоду.

Ключові слова: вагітність; плацента; репродуктивні втрати; ^{137}Cs; віментин; раково-ембріональний антиген (РЕА).

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