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THE FERTILITY OF RATS FEMALES-OFFSPRING BORN TO MOTHERS WITH FETOPLACENTAL INSUFFICIENCY*

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Nowadays, the negative consequences of the xenobiotics's influence on the human and animal reproductive function have been proved by numerous experimental and clinical researches the results of which were represented in the informative overviews. Now, xenobiotics present everywhere (air, soil, water, food, drugs) and it means the high probability of the xenobiotics intake into the organism [1]. The penetration of the toxic substances into mother's organism leads to the cumulative xenobiotic burden of different degree with the following induction of the removal reactions and developing of the obstetric complications, and may cause the metabolic form of fetoplacental insufficiency (FPI) [2]. This condition of pregnant woman may evidence the depletion of the compensatory mechanisms of the fetoplacental complex (FPC) and may finish by prenatal fetus death or cause sick baby birth. The pathogenesis of the FPI is determined by morphological changes and disturbances of placenta functioning. The morphological substrates of placental insufficiency are changes linked with the disturbances of implantation and placentation. The sign of FPI is the disbalance between synthesis of hormones and fetal growth factors of FPC (estrogens, progesterone, placental lactogen, etc) [3–5]. The hormonal disbalance in the prenatal period of the ontogenesis causes substantial modifying influence on the developing of neuroendocrine regulatory mechanisms of sexual behaviour, reproductive processes and reactivity of hypothalamic-pituitary-gonadal axis. These changes occur on the base of mechanisms of hormonal and neuromediatorial imprinting and associate with the epigenetic control disturbances of the cell genome expression [6]. All the changes during the embryonic period of ontogenesis listed above may result in the negative consequen-

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ces in developing and functioning of different systems and organs in the postnatal period of life. It is well known now that children born to mothers with FPI suffer on the cardio-vascular diseases [7], have pathological changes in kidneys [8], brain [9], lungs [10] and in liver. During studying of long-term effects of FPI, different disturbances of physical and intellectual development, which may cause arterial hypertension, diabetes mellitus, metabolic syndrome and other diseases in future, have been observed [5].

As for reproductive system of offspring born to mothers with FPI, there were single investigations which reported about sexual developing and hormonal status of male children, but the given data were controversial and non-comparable due to different procedures of hormone determination and FPI interpetation [11, 12]. As for female offspring, it has been determined that ovaries structure of offspring born to mothers with complicated pregnancy, corresponds to hypoplastic type and testifies low functional activity of fetal gonads, which may lead to further disturbances of germinative function of woman organism [13].

It is proved now, that giving birth after 35 has often caused the pregnancy complications. It is important to consider, because during last decades in the high developed countries the average age of women, who give birth the first time has gradually increased [14]. According to the literature data, the substantial part of such pregnancies is complicated by FPI [15]. Indeed, these women need the treatment or prophylaxis by many drugs. Simultaneous taking a large number of drugs, even in the therapeutic doses, demonstrates series of different disadvantages. That's why, the using of a single medicine in one pharmaceutical dosage form, which combines all the required active pharmaceutical ingredients in well-balanced doses influencing some links of pathogenesis and has a few side effects, is advisable for treatment of women with FPI.

Thus, the purposes of this work were to study influence of further consequences of experimental FPI in mothers of young and mature reproductive age on the females-offspring fertility and to investigate the protective properties of original pharmaceutical composition (PhC).

MATERIALS AND METHODS

The investigation has been carried out according to the National «General Principles for Animal Research Ethics» (Ukraine, 2001), which corresponds to the «European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes» (Strasburg, 1985), and «Principles for Ethic Committee», 2012. Experimental animals have been kept in standard conditions of vivarium of SI «V. Danilevsky Institute for Endocrine Pathology Problems of NAMS of Ukraine», under natural sources of light, standard feeding and water regime ad libitum.

The healthy, Vistar mature rat's females of young (3 months) and mature (10 months) reproductive age with normal four-to-five day's estrus cycles have been used in the experiment. The presence of the sperm cells in morning vaginal swabs has been considered to be the first day of pregnancy. 8 groups for 7 pregnant females in each have been formed: groups 1 and 2 — intact animals of young and mature reproductive age; groups 3 and 4 — females with experimental FPI of young and mature reproductive age accordingly; groups 5 and 6 — young and mature animals with experimental FPI treated by pharmaceutical composition, which contains nonfetotoxic active pharmaceutical ingredients of FPI basic therapeutic group — amino acid (L-arginine), dicarbonic acid (succinic acid), vitamins (folic acid) and vasoactive drug (Dipyridamole). Experimental animals of groups 5 and 6 have received treatment from 11 to 19 day of pregnancy. Groups 7 and 8 — young and mature animals with experimental FPI treated by drug of comparison — Dipyridamole. The modeling of FPI has been fulfilled by daily subcutaneous introduction of 50% tetrachloromethane oil solution in dose of 2 ml/kg of body mass from 12^{th} to 18^{th} day of pregnancy [16].

The fertility of females has been determined according to the results of mating with intact healthy males. The mating in offspring has been fulfilled at the age of 4 months. The presence of sperm cells in morning vaginal

swabs has been considered to be the first day of pregnancy. The fertilization index (ratio of fertilized females to general number of females in group) and pregnancy index (pregnant females-to-fertilized females ratio) have been calculated. Females have been killed on the 20th day of pregnancy. The ovaries and uteruses have been removed. The number of pregnancy's corpus luteum in ovaries and quantity of implantation sites and fetuses in uterus have been calculated. The level of pre-implantation, post-implantation loss and total fetal losses has been determined [17]. According to the results of mating with intact males, the integral index of average realized fecundity (fertility) of rat's females has been calculated ($F_i \pm S_{fi}$) [18].

The blood serum samples have been obtained for Estradiol (E_2) and Testosterone (T) levels determination. The serum blood samples have been stored at temperature — –18°C before analysis. Sex hormones levels have been determined using test-sets «Estradiol-IFA» and «testosterone -IFA» (LLC «Chema», Kyiv).

Determination of the characteristic's distribution in samples has been carried out using Kolmogorov-Smirnov criterion, n — number of animals in each group; Me — median; Q_1 — the first quartile; Q_3 — the third quartile; P — statistical significance among groups according to Dann and Newman–Keuls criteria. The verification of the statistical hypothesis has been fulfilled at significance level ($p < 0,05$).

RESULTS AND THEIR DISCUSSION

It is well known that the reliability of reproductive system functioning is provided by complex of regulating mechanisms, the leading elements of which are hormones synthesized in the organs of hypothalamic-pituitary-gonadal axis. The concentrations of sex hormones have been determined in all of investigated females-offspring.

The different essential levels of E_2 have been observed during comparing intact groups of offspring-rats born to mothers of both age groups. Thus, E_2 concentration has decreased by 62% in females born to mothers of mature reproductive age comparing with offspring born to young mothers. The T level hasn't changed, but ratio of T to E_2 in blood serum has substantial increased ($P < 0,05$) in females born to mature mothers comparing with females born to young mothers (Tabl. 1). It may be explained by decreased hormones levels in women who get pregnant in mature reproductive age due to gradual declining of reproductive function comparing with young women [19].

During sex hormones determination, the reliable increasing of E_2 level by 25% and T level by 122% has been observed in offspring-females born to mothers of young reproductive age with FPI. The ratio between sex hormones levels hasn't differed from intact group of relevant age. After introduction drug of comparison Dipyridamole to pregnant rats with FPI, the increased T level and its substantial increased ratio to E_2 ($P < 0,05$) in blood of mature offspring have been observed. It points out the enlargement synthesis of androgens in females-offspring.

The offspring born to mothers of mature reproductive age with FPI have demonstrated statistically significant ($P < 0,05$) increasing of indices in ratio T/E_2 whilst E_2 concentration was unchanged and T hormone level was a bit more ($P < 0,05$) (Tabl. 1). PhC and Dipyridamole have caused the normalization of sex hormones levels in blood of this group offspring.

Therefore, The FPI in mothers has caused some consequences in their females' offspring: almost all the groups have demonstrated disturbances of hormonal homeostasis manifested by hyperandrogenia in females-offspring. As it is known, exactly this pathology is linked with menstrual cycle disturbances and infertility in women.

All the females-offspring has been mated with intact males in the proestrus period. The fertilization index was 100%, which means the presence of sperm cells in the vaginal swabs in all the females of intact group as well as in females of experimental group, but females born to mothers of both groups of age with FPI have fertilization index decreased by 20%. The mating in intact females has lead to pregnancy in 100% cases. As shown in table 2, pregnancy index in rat's females born to mothers with FPI has decreased comparing with intact control ($P < 0,05$).

Table 1

The indices of concentrations of sex hormones in 160-days females-offspring born to intact and experimental mothers, Me [Q_1 – Q_3]

Group of offspring (n = 7)	Index		
	Estradiol, nmol/l	Testosterone, nmol/l	Ratio T/E_2, SU
Young mother's offspring			
Intact	0,65 [0,50–0,70]	0,90 [0,90–1,30]	1,83 [1,34–2,19]
Born to mothers with FPI	0,90 [0,90–0,90][a]	2,70 [2,70–2,70][a]	5,40 [5,40–5,40][a]
Born to mothers with FPI + Dip.	0,50 [0,40–0,60]	2,00 [2,00–2,00][a]	2,33 [2,25–3,83][a]
Born to mothers with FPI + PhC	0,50 [0,50–0,50]	1,10 [0,90–1,50]	2,22 [2,22–2,22]
Mature mother's offspring			
Intact	0,20 [0,20–0,24][b]	0,90 [0,90–1,00]	4,50 [4,13–4,50][b]
Born to mothers with FPI	0,25 [0,20–0,38]	2,70 [1,70–2,70][c]	7,00 [6,75–8,88][c]
Born to mothers with FPI + Dip.	0,20 [0,20–0,20]	0,90 [0,90–1,00]	4,50 [4,50–4,88]
Born to mothers with FPI + PhC	0,25 [0,20–0,30]	1,10 [0,90–1,10]	4,75 [3,00–5,50]

Notes:

[a] probability of differences among indices in groups 1 and 2, 3, 4; $p < 0,05$;

[b] probability of differences among indices in groups 1 and 5; $p < 0,05$;

[c] probability of differences among indices in groups 5 and 6, 7, 8; $p < 0,05$.

Table 2

Fertilization indices of females-offspring born to mothers with FPI

Index	Group of offspring, number of animals			
	Born to intact mothers (n = 8)	Born to mothers with FPI (n = 8)	Born to mothers with FPI + Dip. (n = 8)	Born to mothers with FPI + PhC (n = 10)
Offspring born to young mothers				
Fertilization index, %	100	80*	100	100
Pregnancy index, %	100	62,5*	75*	60*
Integral fecundity, Fi, of fetuses	10,9 ± 0,8	1,9 ± 0,2*	3,8 ± 0,4*	2,0 ± 0,2*
Integral fertility, %	100	17,2*	35,1*	18,2*
Offspring born to mature mothers				
Fertilization index, %	100	80*	100	100
Pregnancy index, %	100	71,4*	83,3*	83,3*
Integral fecundity, Fi, of fetuses	9,4 ± 0,8	2,2 ± 0,3*	5,3 ± 0,5*	4,7 ± 0,5*
Integral fertility, %	100	24*	56,1*	50,2*

Notes:

number of animals in group;

* statistical significance of differences comparing with intact group.

Thus, the presence of sperm cells in vaginal swab in females of these groups didn't guarantee pregnancy in contrast to intact rats.

The calculation of integral index F_i (average realized fecundity) which includes the number of fertilized and pregnant females and average number of fetus in pregnant females, has shown animals born to rats with FPI have had significant decreased fecundity (Tabl. 2). As seen from table 2, the integral fecundity in females-offspring born to mothers with FPI was on average decreased by 80 %. Drugs introduced with aim to correct the negative consequences of placental insufficiency, have lead to some increasing of females' fecundity, but haven't reached the indices of intact group.

Table 3

The fertilization indices on the 20th day of pregnancy of offspring born to mothers of young reproductive age with FPI, Me [Q_1 – Q_3]

Group of offspring	Quantity by one female, item			Fetal loss, %		
	Corpus luteuv	Implanta–tion sites	General number of fetuses	Pre–im-plantation	Post–im-plantation	Total
Offspring born to young mothers						
Born to intact mothers (n = 8)	12,00 [11,00–13,00]	11,00 [10,50–12,00]	10,50 [9,75–11,25]	8,01 [0,00–16,08]	4,49 [0,00–8,52]	12,50 [5,77–18,18]
Born to mothers with FPI (n = 6)	8,50 * [8,00–9,00]	5,00 * [5,00–7,25]	5,00 * [5,00–5,75]	37,50 [17,71–42,71]	0,00	37,50 [34,38–42,71]
Born to mothers with FPI+Dip. (n = 4)	10,50 [9,75–11,00]	6,00 [3,50–8,50]	6,00 [3,50–8,50]	37,37 [10,61–67,73]	0,00	37,37 [10,61–67,73]
Born to mothers with FPI+PhC (n = 6)	8,50 [8,00–9,75]	8,00 [7,25–8,00]	7,50 [5,50–8,00]	19,84 [2,78–29,64]	0,00	19,84 [2,78–38,39]
Offspring born to mature mothers						
Born to intact mothers (n = 7)	11,00 [10,00–12,00]	9,00 [9,00–11,00]	9,00 [8,50–10,50]	8,33 [0,00–16,78]	8,33 [0,00–10,10]	15,38 [11,11–17,42]
Born to mothers with FPI (n = 4)	9,50 [8,00–11,25]	7,00 [5,75–8,00]	5,00 [4,00–6,50]	25,00 [0,00–51,14]	22,50 [15,00–27,08]	44,32 [18,75–64,39]
Born to mothers with FPI+Dip. (n = 5)	10,00 [8,00–12,00]	8,00 [7,00–8,00]	7,00 [6,00–8,00]	12,50 [7,69–30,00]	12,50 [0,00–14,29]	37,50 [7,69–40,00]
Born to mothers with FPI+PhC (n = 5)	9,00 [9,00–10,00]	8,00 [7,00–8,00]	7,00 [6,00–7,00]	22,22 [11,11–27,27]	10,00 [0,00–12,50]	33,33 [22,22–36,36]

Notes:
n — the number of animals in group;
Me — median;
Q_1 — the first quartile;
Q_3 — the third quartile;
* — statistical significance of differences comparing with intact group according to Dann criterion.

The reduced in the number of corpus luteum, implantation sites and fetuses (12 ± 0), (11 ± 0), (10,5 ± 0) accordingly, (P < 0,05), have been determined during autopsy in females-offspring born to mothers of young reproductive age with FPI. In all other groups these indices and prenatal losses haven't differed from intact group's data (Tabl. 3).

As it was shown in previous investigation, the offspring born to mothers with FPI have had decreased number of follicles and lowered ovaries masses. The diminished number of corpus luteum and follicles of different degree of maturing, the decreasing of primordial follicles pool, the intensification of follicles atresia have been observed during histological investigation that means the normal process of follicles maturing was changed [20]. It may be explained that the process of ovaries and egg cells development in females-offspring has started just in mother's womb. The disturbances of hormonal balance in the perinatal period of ontogenesis have caused the substantial modifying influence on the formation of neuroendocrine mechanisms of behaviour regulation, reproductive processes and reactivity of hypothalamic-pituitary-gonadal axis. These changes occur on the base of mechanisms of hormonal and neuromediatorial imprinting and associate with the epigenetic control disturbances of the cell genome expression [6].

The sign of hormonal changes when FPI in system "mother-placenta-fetus" is the decreasing of progesterone concentration that leads to increasing of general testosterone in fetus. One of the possible mechanisms of influence on the further offspring developing is activity of mother's androgens which may contribute the programming effect on the placental and/or fetal steroid genesis, in this way initiating changes of androgens level and fetoplacental hormonal homeostasis [21, 22, 23].

It is aware, placenta may transform androgens into estrogens. Therefore, it was possible that the most part of mother's and fetus's androgens metabolize just in placenta. This mechanism protects pregnant women as well as female fetuses from virilization. Androstendion and testosterone are high affinity substrates for placental ferment system of aromatases and transform into estronum and estradiol accordingly. Dihydrotestosterone isn't substrate for aromatization, but it is metabolizing under the influence of another placental ferments (oxysteroid dehydrogenases) into less active metabolites such as 5α-androstan-3ß, 17ß-diol [24].

The influence of fetus androgens may be diminished by placental aromatization of androgens and producing of estrogens. This hypothesis has been confirmed by finding of virilization in female fetuses under the deficiency of placental aromatase.

However, aromatization, as a rule, is not enough for fetus complete protection from testosterone transmission and this is not sufficiently explains the absence of fetus virilization. The prenatal influence of normal concentrations of androgens during pregnancy does not lead to changes in the ovaries which may cause polycystic ovary syndrome in the adulthood, but it is not the case for complicated by FPI pregnancy.

According to another hypothesis, masculinization and feminization of brain are not realized by androgens, but their metabolites of estrogen (estradiol. estron, catechol estrogens). Fetal serum protein α-fetoprotein (αFP) which binds estrogens with high affinity plays more than neuroprotective role and, moreover, supplies estrogens to the brain cells for female differentiation supporting. α-FP contributes the female brain defense from excessive influence of estrogens. α-FP is needed for estrogen supplying into the brain and, thereby, plays an active role in the differentiation of female. This protein, also, protects female brain from masculinization and defeminization by estrogens which circulate during embryonic development [25].

The changes of α-FP secretion are possible under FPI that may cause birth of females with disturbances in reproductive system development.

Therefore, under the condition of FPI the excessive secretion of androgens as well as estrogens in mothers as well as in fetuses is possible that may cause further defeminization and masculinization of neuroendocrine system of female fetus. These processes lead to the disturbances of ovarian and menstrual cycles, hyperandrogenia and infertility in the reproductively mature age.

CONCLUSION

1. Fetoplacental insufficiency influences the fertility of females-offspring born to mothers of young and mature reproductive age.
2. Females-offspring born to mothers with FPI of young as well as mature reproductive age have demonstrated decreased pregnancy and integral fecundity indices. Mothers of young reproductive age with FPI have had decreased number of pregnancy corpus luteum, implantation sites and fetuses.
3. The introduction of pharmaceutical composition to pregnant females has lead to female birth with normalized levels of sex hormones, nevertheless, animals has demonstrated decreased fecundity.

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The penetration of the toxic substances into mother's organism leads to the cumulative xenobiotic burden of different degree with the following induction of removal reactions and developing of obstetric complications, and may cause the metabolic form of fetoplacental insufficiency. The pathogenesis of the fetoplacental insufficiency is determined by morphological changes and disturbances of placenta functioning. The purposes of this work were to study influence of further consequences of experimental fetoplacental insufficiency in mothers of young and mature reproductive age on the females-offspring fertility and to investigate the protective properties of original pharmaceutical composition.

Materials and methods. The healthy, Vistar mature rat's females of young (3 months) and mature (10 months) reproductive age have been used in the experiment. 8 groups for 7 pregnant females in each have been formed: groups 1 and 2 — intact animals of young and mature reproductive age; groups 3 and 4 — females with experimental fetoplacental insufficiency of young and mature reproductive age accordingly; groups 5 and 6 — young and mature animals with experimental fetoplacental insufficiency treated by pharmaceutical composition from 11 to 19 day of pregnancy. Groups 7 and 8 — young and mature animals with experimental fetoplacental insufficiency treated by drug of comparison – Dipyridamole. The modeling of fetoplacental insufficiency has been fulfilled by daily subcutaneous introduction of 50% tetrachloromethane oil solution in dose of 2 ml/kg of body mass from 12 to 18 day of pregnancy. The fertility of females has been determined according to the results of mating with intact healthy males. The blood serum samples have been obtained for Estradiol and Testosterone levels determination.

Results. Fetoplacental insufficiency influences the fertility of females-offspring born to mothers of young and mature reproductive age. All the groups of females-offspring born to mothers with fetoplacental insufficiency have significantly lowered pregnancy index and integral fecundity. Only in offspring born to mothers of young reproductive age with fetoplacental insufficiency the decreased number of pregnancy corpus luteum, implantation sites and fetuses has been observed. The introduction of pharmaceutical composition to pregnant females has lead to female birth with normalized levels of sex hormones, nevertheless, animals has demonstrated decreased fecundity.

Key words: fecundity of females-offspring, fetoplacental insufficiency, sex hormones, pharmaceutical composition.

ФЕРТИЛЬНОСТЬ САМОК-ПОТОМКОВ КРЫС, РОЖДЕННЫХ ОТ МАТЕРЕЙ С ФЕТОПЛАЦЕНТАРНОЙ НЕДОСТАТОЧНОСТЬЮ

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Проникновение токсических веществ в организм матери приводит к кумулятивной ксенобиотической нагрузке разной степени с последующим индуцированием реакций выведения и развитием акушерских осложнений, а также может вызвать метаболическую форму фетоплацентарной недостаточности. Патогенез фетоплацентарной недостаточности определяется морфологическими изменениями и нарушениями функционирования плаценты. **Целью** данной работы было изучение влияния отдалённых последствий экспериментальной фетоплацентарной недостаточности у матерей молодого и зрелого репродуктивного возраста на фертильность самок-потомков и изучить защитные свойства оригинальной фармацевтической композиции.

Материалы и методы. В эксперименте использовали здоровых половозрелых самок крыс молодого (3 месяца) и зрелого (10 месяцев) репродуктивного возраста. Сформировано 8 групп по 7 беременных самок в каждой: 1-я и 2-я группы — интактные животные молодого и зрелого репродуктивного возраста; 3-я и 4-я группы — самки с экспериментальной фетоплацентарной недостаточностью молодого и зрелого репродуктивного возраста соответственно; 5-я и 6-я группы — молодые и зрелого репродуктивного возраста с фетоплацентарной недостаточностью, получавшие фармацевтическую композицию с 11 по 19 день беременности. Группы 7 и 8 — животные с экспериментальной фетоплацентарной недостаточностью, получавшие препарат сравнения — дипиридамол. Моделирование фетоплацентарной недостаточности проводилось путем ежедневного подкожного введения 50% масляного раствора

тетрахлорметана в дозе 2 мл/кг массы тела с 12 по 18 день беременности. Плодовитость самок определяли по результатам спаривания с интактными здоровыми самцами. Образцы сыворотки крови брали для определения уровней эстрадиола и тестостерона.

Полученные результаты. Фетоплацентарная недостаточность влияет на фертильность самок-потомков, рожденных от матерей молодого и зрелого репродуктивного возраста. У всех групп самок-потомков, рожденных от матерей с фетоплацентарной недостаточностью, значительно снизился индекс беременности и интегральная плодовитость. Только у потомков, рожденных от матерей молодого репродуктивного возраста с фетоплацентарной недостаточностью, наблюдалось снижение количества желтых тел беременности, мест имплантаций и плодов. Введение фармацевтической композиции беременным самкам привело к нормализации уровней половых гормонов, тем не менее, животные продемонстрировали снижение плодовитости.

Ключевые слова: плодовитость самок, фетоплацентарная недостаточность, половые гормоны, фармацевтическая композиция.

ФЕРТИЛЬНОСТІ САМИЦЬ-НАЩАДКІВ ЩУРІВ НАРОДЖЕНИХ ВІД МАТЕРІВ ІЗ ФЕТОПЛАЦЕНТАРНОЮ НЕДОСТАТНІСТЮ

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Проникнення токсичних речовин в організм матері призводить до кумулятивного ксенобіотического навантаження різного ступеня з подальшим індукуванням реакцій виведення і розвитком акушерських ускладнень, а також може викликати метаболічну форму фетоплацентарної недостатності. Патогенез фетоплацентарної недостатності визначається морфологічними змінами та порушеннями функціонування плаценти. **Метою** даної роботи було вивчення впливу віддалених наслідків експериментальної фетоплацентарної недостатності у матерів молодого і зрілого репродуктивного віку на фертильність самиць-нащадків і вивчити захисні властивості оригінальної фармацевтичної композиції.

Матеріали та методи. В експерименті використовували здорових статевозрілих самиць щурів, молодого (3 місяці) і зрілого (10 місяців) репродуктивного віку. Сформовано 8 груп по 7 вагітних самиць в кожній: 1-а та 2-а групи — інтактні тварини молодого і зрілого репродуктивного віку; 3-я та 4-а групи — самки з експериментальної фетоплацентарной недостатністю молодого і зрілого репродуктивного віку відповідно; 5-а та 6-а групи — молоді та зрілого репродуктивного віку з фетоплацентарної недостатністю, які отримували фармацевтичну композицію з 11 по 19 добу вагітності. Групи 7-а та 8-а — тварини з експериментальною фетоплацентарной недостатністю, які отримували препарат порівняння — дипіридамол. Моделювання фетоплацентарної недостатності проводилося шляхом щоденного підшкірного введення 50% масляного розчину тетрахлорметана в дозі 2 мл/кг маси тіла з 12 по 18 день вагітності. Плодючість самиць визначали за результатами спарювання з інтактними здоровими самцями. Зразки сироватки крові брали для визначення рівнів естрадіолу та тестостерону.

Отримані результати. Фетоплацентарна недостатність впливає на фертильність самиць-нащадків, народжених від матерів молодого і зрілого репродуктивного віку. У всіх груп самиць-нащадків, народжених від матерів з фетоплацентарної недостатністю, значно знижався індекс вагітності та інтегральна плодючість. Тільки у нащадків, народжених від матерів молодого репродуктивного віку з фетоплацентарної недостатністю, спостерігалося зниження кількості жовтих тіл вагітності, місць імплантацій і плодів. Введення фармацевтичної композиції вагітним самицям призвело до нормалізації рівнів статевих гормонів, але тим не менш, тварини продемонстрували зниження плідності.

Ключові слова: плодючість самиць, фетоплацентарна недостатність, статеві гормони, фармацевтична композиція.