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THE REPRODUCTIVE PATHOLOGIES OF MALE OFFSPRING BORN TO MOTHERS WITH FETOPLACENTAL INSUFFICIENCY: HORMONE DEPENDENT MECHANISMS OF DEVELOPING AND PROFILAXIS*

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A lot of negative factors influence the reproductive system (RS) of mature woman [1, 2]. One of the results of interaction between pregnant woman's organism and environmental factors is the development of fetoplacental insufficiency (FPI) which recently occurs in 35–70 % of pregnant. The FPI is the symptom complex considerably explains not only the development of pregnancy and childbirth, but also affects the health condition of offspring in different period of their life.

The correlation between influence of different factors that act during pregnancy on the condition and functioning of offspring's systems of organs in the postnatal period has been proved by numerous investigations carried out in recent years [3–5]. It has been shown, that offspring born to mothers with FPI have got morphological and functional disturbances of many systems.

As for RS condition of offspring born to mothers with FPI, there are only isolated reports about changes of sexual maturing and hormonal disbalance in male [6, 7].

The studies of last few years have determined the main part of pregnancy complications including FPI may be caused by penetrating of xenobiotics — chemical substances — from environment into mother's organism. It is now proven that penetration of xenobiotics into mother's organism leads to the total xenobiotic burden of different degree with further induction of reactions of neutralization and FPI development [8].

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Another challenge that explains current demographic situation in the countries of European region during last few decades is the average age growing in women giving berth for the first time, moreover, women over 35 years old represent the significant part of pregnant in the population. As it is well known, the pregnancy at this age frequently leads to FPI development, pre-eclampsia, the declining in the number of normal childbirth and so on [9]. Meanwhile, the reports devoted to the distinction between offspring born to mothers of different reproductive age haven't been found that couldn't give the opportunity to develop the effective methods for prophylaxis of pregnancy complications.

It is preferably to use for FPI treatment the single medicine which has combined all the required active pharmaceutical ingredients in one pharmaceutical dosage form. These active pharmaceutical substances have to be in well-balanced doses, demonstrate the minimal number of side effects and can influence the several chains of pathogenesis.

Therefore, the aims of this investigation were to determine hormone depended mechanisms of reproductive pathologies developing in the ontogenesis of male offspring born to different aged mothers with FPI and experimental grounding of potential preventive activity of developed pharmaceutical composition suitable for animals of this phenotype.

MATERIALS AND METHODS

The investigation has been carried out according to the «National General Principles for Animal Researches Ethics» (Ukraine, 2001), which corresponds to the «European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Strasburg, 1985)» [10] and to the «Principles of Bioethics committees», 2012 [10].

Healthy, mature Wistar rat females of young (3–4 months) and mature (8–10 months) reproductive age with normal four-to-five day's estrus cycle have been used in the experiment. The presence of sperm cells in morning vaginal swabs has been considered to be the first day of pregnancy. Eights groups for 7 pregnant females in each group have been formed: groups 1 and 2 — intact animals of young (Int./young) and mature reproductive age (Int./mature); groups 3 and 4 — young (FPI/young) and mature females with experimental FPI accordingly (FPI/mature); groups 5 and 6 — young (FPI/young+PhC) and mature (FPI/mature+PhC) animals with experimental FPI which have obtained from 11^{th} to 19^{th} day of pregnancy the pharmaceutical composition (PhC) containing nontoxic active pharmaceutical ingredients of the base FPI therapeutic group. The PhC has consisted of amino acid (L-arginine) and dicarboxylic acid (succinic acid), vitamins (folic acid) and vasoactive drug (dipyridamole). Groups 7 and 8 — young (FPI/young + D) and mature animals (FPI/mature + D) with experimental FPI which have obtained drug of comparison — dipyridamole *per os*. Modeling of FPI has been carried out by daily subcutaneous administration of the 50 % tetrachloromethane oil solution in dose of 2 ml/kg of body weight from 12^{th} to 18^{th} day of pregnancy [11].

The physical and sexual development of male offspring have been estimated, on the 50^{th} day of life (puberty) the developing of reproductive system has been determined. Other part of offspring has been raised up to sexual maturity (four months) and their sexual behavior, fertility, spermatogenesis, sex hormones levels, masses and condition of tested organs, testicular samples for histology, the indices of lipoperoxidation (LP) and antioxidative defense system (ADS) have been determined according to the general used methods.

The objects of the investigations were active pharmaceutical ingredients of FPI basic therapeutic group (dipyridamole, L-arginine, succinic and folic acids) and, in particular, pharmaceutical composition (PhC) for oral use in form of hard gelatinous capsules obtained on their base. Each capsule has consisted of dipyridamole (12,50 %), L-arginine hydrochloride (10,00 %), folic acid (0,125 %), succinic acid (62,50 %) and excipient — silicium dioxide (0,25 %) as a glidant, vehicle — corn starch, pregelatinized corn starch or microcrystalline cellulose the rest. The acute toxicity of PhC has been estimated [12, 13].

Parametric and nonparametric tests have been used. The Kolmogorov-Smirnov test has

been used for estimation of normality of the distribution. One-way analysis of variance (ANOVA) and Student-Newman-Keils test have been used for comparing differences in samples with normal distribution. Mann–Whitney U-test has been used for comparing two sets of samples with non-normal distribution, for multiple comparisons – *Kruskal–Wallis* H-*test* and *Dunn's test*. Data have been represented as arithmetic mean ($\bar{X}$) and sample standard deviation ($S_{\bar{X}}$); Me — median; Q_1 — the first quartile; Q_3 — the third quartile. The differences have been considered to be reliable at significance level $p < 0,05$.

RESULTS AND THEIR DISCUSSION

During baby-rats testing the physiological indices of somatic development which are considered to be the indications of normal animals' physical condition have been estimated. The FPI has had minimal effect on the somatic development of offspring born to mothers of young reproductive age. In contrast, offspring born to mature mothers have demonstrated delaying eyes opening by 66 %, the appearing of primary hair has been delayed by 40 % and secondary hair — by 28 % ($p < 0,01$), respectively. Thus, the FPI impacts the somatic development of males' offspring.

While researching the testosterone level of male offspring born to mothers with FPI of both groups of age on the 5th day of life, it has been determined testosterone level decreased comparing with intact animals ($p < 0,01$). The introduction of PhC and dipyridamole to pregnant animals of young and mature reproductive ages hasn't caused significant increase in testosterone level (Table 1).

It can be argued that FPI impacts the sex differentiation of male offspring's brain. The results of investigations have confirmed the role of «Testosterone peak» on the 5th day of life in forming of RS's neuroendocrine regulation during early ontogenesis and in the pathogenesis of its disturbance due to hormonal disbalance. This condition will further lead to delaying of sexual maturity in the form of postponed testicles moving to the scrotum. The normal terms of sexual maturity have been observed in male offspring of FPI/mature + PhC group.

During investigation of masses of reproductive organs, the decreasing of prostate gland (PG) mass by 40 % in offspring of the FPI/young group has been observed. Male offspring of FPI/young + D group have demonstrated decreasing in PG mass by 32 %, but PG mass in FPI/mature + D group of offspring has increased by 27 % ($p < 0,05$). The pharmaceutical composition has led to the normal development of PG.

Table 1

Testosterone level in blood serum of male offspring on the 5th day of life, n = 7, ($\bar{X} \pm S_{\bar{X}}$)

Group of offspring	Testosterone, nmol/l	P-value
1. Int./young	24,0 ± 1,0	—
2. FPI/young	16,3 ± 0,7	$p_{1-2} < 0,05$
3. FPI/young + PhC	20,4 ± 1,3	$p_{1-3} < 0,05$ $p_{2-3} < 0,05$
4. FPI/young + D	19,7 ± 1,3	$p_{1-4} < 0,05$ $p_{2-4} < 0,05$
5. Int./mature	24,9 ± 1,1	—
6. FPI/mature	17,9 ± 1,0	$p_{5-6} < 0,05$
7. FPI/mature + PhC	19,1 ± 1,3	$p_{5-7} < 0,05$
8. FPI/mature + D	21,3 ± 1,0	$p_{5-8} < 0,05$ $p_{6-8} < 0,05$

Note:
p — significance level of difference between groups.

Table 2

Sex hormones levels in blood serum of male offspring, n = 10, Me [Q_1–Q_3]

Group of offspring	Index		
	Estradiol, nmol/l	Testosterone, nmol/l	Ratio T/E_2, SU
Young mothers			
1. Int./young	0,20 [0,20–0,40]	23,00 [22,00–23,10]	110,00 [50,83–115,00]
2. FPI/young	0,60 [0,50–0,70] p_{1-2}< 0,05	13,80 [4,00–15,00] p_{1-2}< 0,05	17,25 [10,00–25,00] p_{1-2}< 0,05
3. FPI/young + D	0,50 [0,50–0,50] p_{1-3}< 0,05	4,00 [3,50–4,00] p_{1-3}< 0,05 p_{2-3}< 0,05	7,00 [6,67–8,00] p_{1-3} < 0,05 p_{2-3}< 0,05
4. FPI/young + PhC	0,60 [0,20–0,60] p_{1-4} < 0,05	25,00 [25,00–32,30] p_{2-4} < 0,05 p_{3-4} < 0,05	49,00 [41,67–125,00] p_{2-4} < 0,05 p_{3-4} < 0,05
Mature mothers			
1. Int./mature	0,50 [0,50–0,60]	15,00 [8,30–15,00]	24,75 [16,60–30,00]
2. FPI/mature	0,50 [0,40–0,50]	9,10 [7,80–10,00] p_{1-2}< 0,05	15,67 [15,60–20,00]
3. FPI/mature + D	0,30 [0,30–0,30] p_{1-3}< 0,05 p_{2-3}< 0,05	3,00 [2,30–3,00] p_{1-3}< 0,05 p_{2-3}< 0,05	10,00 [7,67–10,00] p_{1-3}< 0,05 p_{2-3}< 0,05
4. FPI/mature + PhC	0,50 [0,50–0,60] p_{3-4}< 0,05	2,00 [0,90–2,00] p_{1-4}< 0,05 p_{2-4}< 0,05 p_{3-4}< 0,05	4,00 [2,25–4,00] p_{1-4}< 0,05 p_{2-4}< 0,05 p_{3-4}< 0,05

Note:
p — statistical significance of differences among groups.

During investigation of offspring hormone status in the FPI/young group the increase in estradiol level by 200 % and decrease in testosterone by 40 % has been determined. The introduction of PhC to young pregnant animals with FPI has led to the normalization of testosterone level in males of puberty age (Table 2).

The offspring of FPI/mature group has had testosterone level decreased by 60 % ($p < 0,05$). Treatment with dipyridamole in pregnant FPI rats did not normalize testosterone levels and potentiated its further reduction (see Table 2).

During investigation of histological samples of testicles of male rats in puberty of FPI/young group, the inhibition of the gonad differentiation has been observed. In particular, the diameter of seminiferous tubules was decreased by 19,63 %, its location was less dense, the lumen was distinct, the thickness of spermatogenic epithelium was decreased by 35,30 % ($p < 0,05$), the thickness of spermatogenic cells pool wasn't more than two layers in the most part of tubules, the spermatogenesis was finished at primary spermatozoa stage. The negative consequences of FPI have been mitigated in FPI/mature group and process of spermatogenesis development has been similar to intact animals.

Thereby, FPI has led to the inhibition of gonad differentiation only in animals of FPI/young group. The introduction of PhC to the young pregnant females with FPI has activated proliferation and differentiation of spermatogenic epithelium in their offspring which has led to the appearance of matured sperm cells in the part of seminiferous tubules. Thus, proposed PhC has helped to recover the terms of offspring spermatogenesis development to the level of dipyridamole group.

The next part of the research was to determine the influence of FPI on the oxidative stress development in the both sex offspring at puberty. FPI causes the modification of AOD enzymes activity in rat offspring at puberty

Table 3

Sex hormones levels in blood serum of male offspring, n = 10, Me [Q_1–Q_3]

Group of offspring	Index		
	Estradiol, nmol/l	Testosterone, nmol/l	Ratio T/E_2, SU
1. Int./young	0,30 [0,30–0,40]	13,00 [9,00–14,90]	37,25 [30,00–37,50]
2. FPI/young	0,60 [0,20–0,60] p_{1-2}< 0,05	8,00 [8,00–8,00] p_{1-2}< 0,05	13,33 [13,33–35,00] p_{1-2}< 0,05
3. FPI/young+D	0,40 [0,40–0,50] p_{1-3}< 0,05	7,00 [7,00–7,00] p_{1-3}< 0,05	17,50 [14,00–17,50] p_{1-3}< 0,05
4. FPI/young + PhC	0,60 [0,30–0,60] p_{1-4}< 0,05	8,00 [7,00–8,00] p_{1-4}< 0,05	13,33 [13,33–23,33] p_{1-4}< 0,05
5. Int./mature	0,30 [0,30–0,60]	10,00 [9,35–10,00]	26,67 [20,00–31,17]
6. FPI/mature	0,50 [0,40–0,50] p_{5-6}< 0,05	8,00 [8,00–9,00] p_{5-6}< 0,05	18,00 [17,50–18,00] p_{5-6}< 0,05
7. FPI/mature + D	0,20 [0,20–0,20] p_{5-7}< 0,05	7,00 [7,00–8,00] p_{5-7}< 0,05	35,00 [35,00–35,00] p_{5-7}< 0,05
8. FPI/mature + PhC	0,60 [0,50–0,60] p_{5-8}< 0,05	7,00 [7,00–8,00] p_{5-8}< 0,05	13,33 [11,67–14,00] p_{5-8}< 0,05

Note:
p — probability of differences among indices in this group.

that is manifested in changing of blood levels of primary LP products as well as LP end-products. Thus, it can be noted that FPI caused considerable changes of AOD enzymes activity in male offspring.

During studying mature males, it has been determined that FPI has led to the changes of testosterone, estradiol levels and has shifted sex hormones ratio to the hyperestrogenemia in the all of offspring (Table 3).

Rats' autopsy has been carried out and after complex of investigation body masses and relative organs' masses have been calculated. It has been determined FPI has to a large extent influenced male offspring born to mothers of mature reproductive age. The decreasing in relative mass of pituitary gland by 20 % has been observed in FPI/young group of animals. FPI/young + D group of rats has demonstrated thymus mass decreased by 23 %. The introduction of PhC hasn't affected the pituitary gland masses increasing in contrast to dipyridamole.

The increasing in masses of reproductive organs in offspring of FPI/mature group has been statistically proven as follows: PG mass — by 36 % and epididymides — by 23 % ($p < 0,05$), accordingly. Conversely, mass of adrenal glands has decreased by 34 % comparing with group of intact animals of appropriate age. The decrease in masse of thymus by 35 % and adrenal gland by 32 % comparing with intact animals has been detected in FPI/mature + D group. These changes have occurred at the statistically significant increasing of rats' body masses by 19 % ($p < 0,05$) and PhC has promote the recovering of almost all mass indices of tested organs. Also, masses of spleen, testicles, liver and seminal vesicles have been researched but the substantial differences in their values haven't been detected.

The spermogram indices of male offspring were determined during autopsy. The number of pathological forms of sperm cells has decreased by 43 % ($p < 0,05$) in FPI/young

group of animals according to indices of functional condition of epididymal sperm cells. But, amid declining in number of pathological cells of spermatogenesis, the signs of agglutination have been detected in 40 % of animals ($p < 0,05$).

During spermogram investigation of FPI/mature group the decreasing of number of motile sperm cells by 40 % ($p < 0,05$) and sperm cells by 37 % ($p < 0,05$) has been observed. This has led to declining of concentration of normal spermatozoons comparing with intact group. The agglutination of sperm cells has been also determined in the largest part of this group of offspring (80 %, $p < 0,05$), and agglutination was more expressed. The introduction of PhC and dipyridamole has caused normalization of spermogram in those animals.

During histological researche, disturbances in the structure of testicles and signs of spermatogenesis delaying haven't been determined.

The researching of sexual behavior of FPI/young group rats has revealed the time for copulatory reactions restoring was increased, but the number of approaches has been decreased by 35 % and intromissions — by 39 % ($p < 0,05$). During this test only 20 % of males of this group have had ejaculation. After treating by PhC of young females with FPI the number of their male offspring with ejaculation was bigger and practically equal to control group (90 % with frequency of ejaculation ($0,9 \pm 0,1$) per test), although hourly and quantitative indicators haven't reached intact group level. The indices of sexual behavior in FPI/young + D group haven't differed from FPI/young group.

During investigation of sexual behavior of FPI/mature group's offspring the increasing of time for restoring the copulatory reactions has been detected, in contrast, the number of approaches and intromissions has decreased by half, the number of male to female approaching has increased by 40 % ($p < 0,05$). It has been noted that only 30 % of males have finished coitus in the allotted time by ejaculation. An increasing number of males of FPI/mature+PhC group have had time to finish the coitus by ejaculation (80 %, with frequency ($0,8 \pm 0,1$)), latent and quantitative indices of sexual behavior have remained on the pathology level. Dipyridamole hasn't caused any effect on the male offspring sexual behavior violated due to FPI.

The index of pregnancy has amounted to 100 % after mating of males of Int./young group with intact females, in FPI/young group of males this index was 83,3 %. The integral fecundity index (Fi) in FPI/young group has amounted to ($4,2 \pm 0,6$) fetuses per one female (69 %), in FPI/young group — ($4,4 \pm 0,5$) fetuses (73,5 %), in FPI/young+PhC group — ($7,0 \pm 0,7$) fetuses (100 %) ($p < 0,05$) comparing with intact animals which have had Fi index ($6,0 \pm 0,8$) fetuses per one female (100 %).

The fertilization index has been decreased by 50 % in animals of FPI/mature group, in FPI/mature + D — by 17 % and in FPI/mature + PhC — by 15 % to compare with intact group of rats. The pregnancy index has amounted to 75 % in FPI/mature group and 80 % in FPI/mature + D group that was significantly less than in FPI/mature + PhC and control group — 100 % ($p < 0,05$). The integral fertility of males was decreased only in FPI/mature and FPI/mature+D groups — by 88 % and 63 %, accordingly ($p < 0,05$).

Summarizing results set out in the article, it may be noted that FPI in females in third trimester of pregnancy leads to marked changes in RS of their male offspring born to mothers of reproductively young and reproductively mature age. Data obtained indicate the opportunity and ways to develop the medicines for prophylaxis of reproductive pathologies in children born to mothers with FPI.

CONCLUSIONS

1. The presence of fetoplacental insufficiency in mothers of different reproductive age leads to birth of male offspring which have testosterone level decreased average by 30 % in the period of sex differentiation of brain that causes disturbances of somatic and sexual development of animals in the early ontogenesis.
2. The studying of puberty genesis of male offspring has shown disbalance of sex hormones, the decrease in testosterone in all the animals, and increase in estradiol level

have been observed only in rats born to reproductively young mothers. More marked changes of morphological structure of testicles and inhibition of sperm cells differentiation have been detected in this group of animals during morphological researches. Fetoplacental insufficiency causes significant changes of antioxidative defense system in male offspring, more marked changes have been observed in offspring born to mothers of mature reproductive age.

3. The hormonal disbalances, the relative estrogenization, the deterioration of spermatogenesis and sexual behavior and integral fertility's declining have been detected in mature male offspring born to mothers with FPI.
4. Developed pharmaceutical composition has demonstrated positive influence on the somatic and sexual development of male offspring; it has led to normalization of prooxidative-antioxidative balance and hormonal state, to enhancing of sexual behavior and spermogram improvement in male offspring. The efficacy of prophylactic activity of pharmaceutical composition has exceeded drug of comparison dipyridamole that has been proven by morphological, physiological, biochemical and enzyme immunoassay methods of investigation.

REFERENCES

1. Hart RJ. *Physiol Rev* 2016;96(3): 873-909. https://doi.org/10.1152/physrev.00023.2015. PMID: 27252278.
2. Shho varto znaty pro reproduktyvne zdorov'ja, available at: *https://phc.org.ua/news/scho-varto-znati-pro-reproduktivne-zdorovya.*
3. Barker DJ, Thornburg KL. *Placenta* 2013;34: 841-845. https://doi.org/10.1016/j.placenta.2013.07.063.
4. Burton GJ, Jauniaux E. *Am J Obstet Gynecol* 2018; 218(2S): S745-S761.
5. Bekmukhambetov Y, Mamyrbayev A, Dzharkenov T, et al. *Am J Reprod Immunol* 2016;76(4): 299-306. https://doi.org/10.1111/aji.12544.
6. Pampanini V, Germani D, Puglianiello A, et al. *J Endocrinol* 2017;232(2): 247-257.
7. Salonia A, Rastrelli G, Hackett G, et al. *Nat Rev Dis Primers* 2019;5(1): 38. https://doi.org/10.1038/s41572-019-0087-y.
8. Erickson AC, Arbour L. *J Environ Public Health* 2014; 2014: 901017. https://doi.org/10.1155/2014/901017.
9. Patel R, Moffatt JD, Mourmoura E, et al. *J Physiol* 2017; 595(6): 2065-2084. https://doi.org/10.1113/JP273350.
10. Spisok podpisanij i ratifikacij Dopolnitel'nogo protokola k Evropejskoj konvencii o zashhite zhivotnyh pri mezhdunarodnoj perevozke, available at: http://zakon4.rada.gov.ua/laws/main?find=1&sp=i&user=c393&text=%F2%E2%E0.
11. Jakovljeva LV, Zajchenko GV, Cypkun AG, et al. Doklinichne vyvchennja likars'kyh zasobiv, pryznachenyh dlja likuvannja placentarnoi' dysfunkcii': metodychni rekomendacii', *Kyi'v,* 2009.
12. Seljukova NJu, Kustova SP, Kudrja MJa, et al. *Ukr Biofarmacevtych Zhurn* 2020;4(65): 35-39.
13. Patent 143079. Farmacevtychna kompozycija dlja korekcii' porushen', shho vynykajut' za umov fetoplacentarnoi' nedostatnosti.

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Introduction. Fetoplacental insufficiency (FPI) is the symptom complex that substantially results not only in pregnancy development and childbirth, but in the health condition of offspring at different times. It has been shown that offspring born to mothers with FPI have morphological and functional disturbances of different systems of organs. The aims of this research were to determine hormone depended mechanisms of reproductive pathologies developing in the ontogenesis of male offspring born to different aged mothers with FPI and experimental grounding of potential preventive activity of developed pharmaceutical composition suitable for animals of this phenotype.

Materials and methods. Mature Wistar rat females of young (3–4 months) and mature (8-10 months) reproductive age have been used in the experiment. Eights groups for 7 pregnant females in each group have been formed. Modeling of FPI has been carried out by daily subcutaneous administration of the 50 % tetrachlo-

romethane oil solution at dose of 2 ml/kg of body weight from 12th to 18th day of pregnancy. The reproductive system of male offspring has been estimated.

Results. FPI influences the sex differentiation of brain in male offspring that reflects in delaying of sexual maturity in the form of postponed testicles moving to the scrotum. FPI leads to relative estrogenization, inhibition of sperm cells differentiation and causes significant changes in antioxidant defense system in male offspring at puberty. FPI causes changes of testosterone, estradiol levels and shifts sex hormones ratio to the hyperestrogenemia in the all of mature male offspring that influence the activity of male sexual behavior, worsens spermogram and fertility.

Conclusion. Fetoplacental insufficiency in females in third trimester of pregnancy leads to marked changes in reproductive system of their male offspring born to mothers of reproductively young and reproductively mature age. Data obtained indicate the opportunity and ways to develop the medicines for prophylaxis of reproductive pathologies in children born to mothers with fetoplacental insufficiency.

Keywords: fetoplacental insufficiency, male offspring, reproductive disease, hormonal status, pharmaceutical composition.

РЕПРОДУКТОПАТІЇ НАЩАДКІВ ЧОЛОВІЧОЇ СТАТІ МАТЕРІВ ІЗ ФЕТОПЛАЦЕНТАРНОЮ НЕДОСТАТНІСТЮ: ГОРМОНАЛЬНОЗАЛЕЖНІ МЕХАНІЗМИ РОЗВИТКУ ТА ПРОФІЛАКТИКА

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Вступ. Фетоплацентарна недостатність (ФПН) – симптомокомплекс порушень, який значною мірою обумовлює не тільки перебіг вагітності та пологів, але й стан здоров'я народженого нащадка у різні періоди його життя. Показано, що нащадки, які були народжені матерями із ФПН, мають морфофункціональні порушення з боку багатьох систем. **Метою** дослідження було визначення гормонально залежних механізмів розвитку репродуктопатій в онтогенезі нащадків щурів чоловічої статі, народжених від матерів різного віку із фетоплацентарною недостатністю, та експериментальне обґрунтування потенційної профілактичної дії розробленої оригінальної фармацевтичної композиції щодо фенотипу таких тварин.

Матеріали та методи. В експерименті були використані зрілі самиці щурів Wistar молодого (3–4 місяці) та зрілого (8–10 місяців) репродуктивного віку. Було сформовано вісім груп по 7 вагітних самок у кожній групі: Моделювання ФПН проводили шляхом щоденного підшкірного введення 50 % розчину олії тетрахлорметану в дозі 2 мл/кг маси тіла з 12 по 18 день вагітності. У тварин-нащадків чоловічої статі оцінювали стан репродуктивної системи.

Результати. ФПН впливає на статеве диференціювання мозку у нащадків-самців, що реалізується у затримці статевого розвитку в вигляді більш пізніх термінів опущення сім'яників. У пубертатному віці ФПН призводить до відносної естрогенізації, гальмування диференціювання статевих клітин, викликає суттєві зміни активності базових елементів антиоксидантного захисту у нащадків чоловічої статі. У статевозрілих самців щурів ФПН призводить до вірогідних змін у рівнях загального тестостерону, E_2 та зсуву співвідношення статевих гормонів у бік гіперестрогенізації у всіх нащадків, що впливає на зниження рівня статевої чоловічої поведінки, спермограми та фертильності.

Висновок. Фетоплацентарна недостатність самиць щурів у третьому триместрі вагітності призводить до виразних змін в репродуктивній системі нащадків чоловічої статі, які були народжені матерями репродуктивно молодого та зрілого віку. Отримані дані вказують на можливість та шляхи створення засобів профілактики репродуктопатій у дітей, народжених матерями із фетоплацентарною недостатністю.

Ключові слова: фетоплацентарна недостатність, нащадки чоловічої статі, репродуктопатії, гормональний статус, фармацевтична композиція.