

## THE IMPACT OF CHOLECALCIFEROL ON THE REPRODUCTIVE SYSTEM FUNCTION IN RAT MALES WITH EXPERIMENTAL GONADOPATHY\*

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The creating of safe medicines or developing of treatment schemes that haven't androgenic activity, but stimulate the functioning of reproductive system without negative side effects have the importance for improvement of reproductive ability of people as well as of animals. Thereby, herb medicines such as Tribestan® (Tr) and vitamins, in particular, vitamin D which has the properties of vitamin, but demonstrates commonly agreed hormonal mechanisms of activity, nowadays draw the attention of researches. [1–3].

It is well known, the VDR receptors (vitamin D receptors) are situated almost in the all of organs and tissues of reproductive system. They were found in testicles cells and in the sperms [4]. D-deficiency statuses may be occurred under the condition of hypofertility of

different genesis. Thus, Klaus Peter Dikmann et al. (2021) have reported significant transitional declining of cholecalciferol level after orchietomy [5]. Nowadays, it is proved, that testicle is one of the sites when the precursor of vitamin D transforms into its active form [4]. There are data, that vitamin D has positive influence on sex behaviour and functional properties of sperms [6, 7]. Vitamin D<sub>3</sub> (cholecalciferol) demonstrates inhibitory effect on the excess inflammatory biomarkers and also regulates the expression of reproductive genes and androgens' synthesis in testicles [8]. At the same time, other experimental works haven't determined the connection between vitamin D level and testicles functioning, which may be explained by differences in the design of experiments such as age, body mass index and es-

\* The work was performed in the State Institution «V. Danilevsky Institute for Endocrine Pathology Problems of the National Academy of Medical Sciences of Ukraine» within the framework of the topic «Determination of vitamin D deficiency and insufficiency in the development of sex glands dysfunction, the grounding of treatment» (State registration number: 0119U102387).

The institution that finances the study is the National Academy of Medical Sciences of Ukraine.

The authors assume responsibility for the published work.

The authors guarantee absence of competing interests and their own financial interest when carrying out the research and writing the article.

The manuscript was received by the editorial staff 05.07.2022.

sential vitamin D level. Other than vitamin D influence on the sperm indices, the most part of investigations accepts the ability of vitamin D to improve men's reproductive capacity, in particular, sperms motility increasing. As for courses of pregnancies which were obtained from persons with different vitamin D level, they were much better in those with normal vitamin content [4].

## MATERIALS AND METHODS

The investigation has been fulfilled on the Vistar 7-month-old rat males of 250–300 g body mass and reproductively matured rat females with normal estrus cycles.

The studying 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) [9]. The rats have been kept in cages singly, under standard conditions of vivarium, natural light sources and daily nutrition recommended for these animals, and water regime *ad libitum* [10]. Sex active males have been divided into such group as: S-model group (animals with experimental model of serotonin damage of gonads, gonadopathy (GP)); S + solvent (rats with experimental gonadopathy which obtained solvent — Apricot kernel oil; after data estimated, these groups were united into group S due to absence of differences between groups); S + vit. D<sub>3</sub> group (animals with experimental serotonin damage of testicles have received vitamin D<sub>3</sub> *per os*); S + Tr (rats with GP which treated with the drug of comparison — Tr); S + vit. D<sub>3</sub> + Tr group (animals with experimental GP treated by cholecalciferol and Tr). Control group has been represented by intact males.

The experimental testicles pathology has been induced by Serotonin hydrochloride introduction (Shan Dong Octagon Chemicals Limited, China), during 14 days subcutaneously, in dose of 3,3 mg/kg body mass [11].

The drug of comparison Tr has been introduced *per os* in dose of 68 mg/kg body mass three days before Serotonin hydrochloride introduction; under the condition of serotonin obtaining (14 days) and during three days

Listed above confirms the actuality of studying the impact of vitamin D and its complex schemes of treatment of pathological changes in testicles and reproductive disturbances

**The aim** of this investigation was to determine the condition of rat males' reproductive system with experimental testicles pathology treated by vitamin D<sub>3</sub>.

after its last injection once a day. During experiment the tablets has been grinded in the mortar to a homogenous mass which has been administrated to experimental rats in amounts calculated based on one tablet mass × 3, the content of active pharmaceutical ingredient in one tablet (750 mg) and rat's dose of 68 mg/kg of body mass. During investigation the dose of medicine has been calculated using coefficient of species resilience on the base of human daily dose. Vitamin D<sub>3</sub> has been given according to the same scheme in value of 0,5 ml in dose of 4000 IU (*per os*). Oil solution of vitamin D<sub>3</sub> was prepared on the base of Apricot kernel oil and vitamin D<sub>3</sub> substance (powder, PRC, lot № CHG20062009 which meets the standards of GB9840-2017).

The male fertility has been determined according to fertility and fecundity indices of rats' females fertilized by experimental rats' males [12]. Due to results of mating with intact females the integral index of average realized fecundity (fertility) of rats' males has been calculated (Fi) [13].

The researches of spermatogenesis have been carried out in epididymis's suspension after animals removing from the experiment using quick decapitation. The sperm concentration, number of sperm cells and its pathological forms have been determined using microscope «Biolam» and according to standard procedure (Horiaev camera). The morphometric indices demonstrating spermatogenesis in the gonads were studied on the histological sections [14].

**Statistical interpretation of data obtained.** The Shapiro–Wilk test has been used to check if the data follows normal distribution. The probability of differences between sets of means has been determined using t-Student test, data performed as sample mean ( $\bar{X}$ ) and its standard

deviation ( $\pm S_x$ ). The Kruskal–Wallis test — nonparametric equivalent of one-way analysis of variance, and then Mann–Whitney U test were used. The standard set of programs «Sta-

tistica 6» has been applied for determination of statistical differences. Differences have been considered to be significant at  $P < 0,05$  [15].

### RESULTS AND THEIR DISCUSSION

The spermogramm indices between S model and S + solvent groups at the end of the experiment haven't statistically differed. That's why the results of these groups were united into group S which was used for comparing data of other groups of animals.

The sperm cells concentration in control group was 46 mln/ml with low percentage of pathological form, 79 % — motile sperms which demonstrated fast forward movement (Table 1). GP was caused by Serotonin hydrochloride's vasoconstricting activity leads to trophic disturbances in testicles tissues which explain pathological changes and spermatogenesis declining [10, 16]. This fact was confirmed by our investigation — serotonin burden leads to statistically significant increasing of all the spermogramm indices (see Table 1).

The declining of motile sperm percentage by 88 % has been detected in S group comparing with Control, general concentration of sperm cells became 75,3 % less and part of pathological forms has raised by 77 % ( $p < 0,05$ ) (Fig. 1). Meanwhile, as histological samples of testicles damaged by serotonin show, the number of spermatogonia has decreased almost double, the index of spermatogenesis has declined at expense of quantity of channels on 12<sup>th</sup> stage of meiosis, the percent of channels with detached epithelium has increased that may explain the disturbance of spermogramm of epididymis'sperm cells in these animals.

The positive influence on the spermatogenesis in testicle as well as in epididymis has been observed when referent drug Tr used. Statistically significant increasing of motile

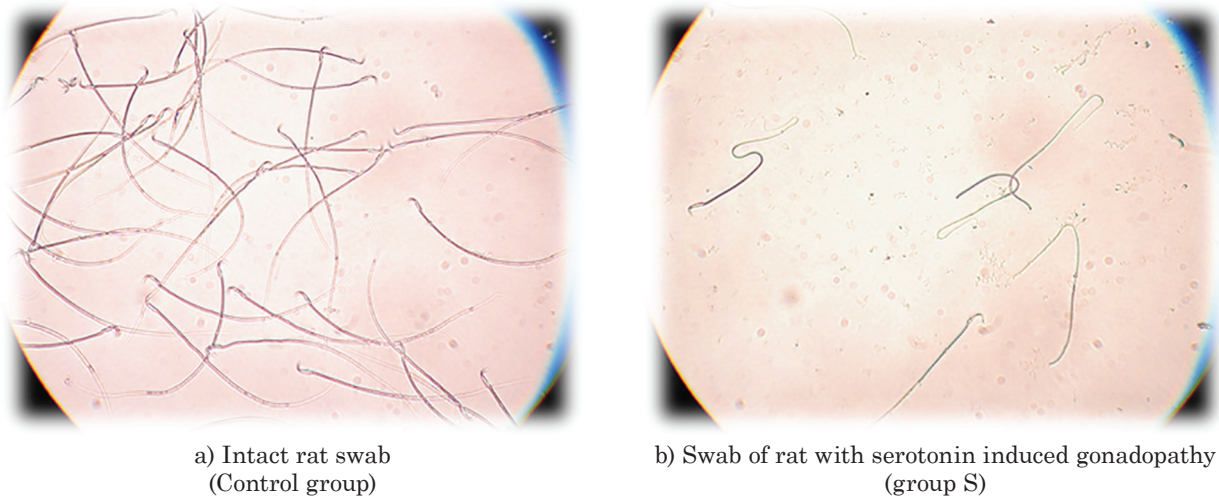
Table 1

Parameters of spermatogenesis in rats with gonadopathy which obtained vitamin D<sub>3</sub>

Indices	Group				
	Control	S	S + Tr	S + vit. D <sub>3</sub>	S + vit. D <sub>3+Tr</sub>
Epididymis					
General concentration, mln/ml, M ± m n	46,00 ± 2,9 5	11,3 ± 2,0 <sup>1)</sup> 12	29,6 ± 3,8 <sup>1)2)</sup> 8	17,4 ± 3,5 <sup>1)3)</sup> 7	23,2 ± 2,0 <sup>1)2)</sup> 8
Percentage of motile sperms, %, M ± m n	78,6 ± 5,1 5	9,8 ± 1,7 <sup>1)</sup> 12	42,0 ± 7,9 <sup>1)2)</sup> 8	21,3 ± 4,6 <sup>1)2)3)</sup> 7	42,6 ± 5,9 <sup>1)2)4)</sup> 8
Pathological forms, %, M ± m n	4,0 ± 0,8 5	17,4 ± 2,0 <sup>1)</sup> 12	6,4 ± 0,9 <sup>2)</sup> 8	12,7 ± 1,9 <sup>1)3)</sup> 7	8,0 ± 1,6 <sup>2)4)</sup> 8
Testicle					
Normal spermatogonia in the channel, (M ± m) n	61.1 ± 0.5 4	26,6 ± 3,4 <sup>1)</sup> 7	50.6 ± 3.2 <sup>2)</sup> 4	49.1 ± 1.9 <sup>1),2)</sup> 4	60.1 ± 0.3 <sup>2)</sup> 4
Index of spermatogenesis score, Me (LQ; UQ) n	3.33 (3.32; 3.34) 4	1.98 (0.23; 2.92) 8	3.0 (2.56; 3.30) 4	3.0 <sup>2)</sup> (2.64; 3.23) 4	3.3 (3.32; 3.33) 4

Notes:

- <sup>1</sup> Statistically significant differences from Control group ( $p < 0,05$ );
- <sup>2</sup> Statistically significant differences from S group ( $p < 0,05$ );
- <sup>3</sup> Statistically significant differences from S + Tr group ( $p < 0,05$ );
- <sup>4</sup> Statistically significant differences from S + vit. D<sub>3+Tr</sub> group ( $p < 0,05$ ).



a) Intact rat swab  
(Control group)

b) Swab of rat with serotonin induced gonadopathy  
(group S)

Fig. 1. Swabs of rat' epididymal sperms,  $\times 400$ .

gametes by 4,3 times and sperms concentration by 2,6 times was noted, but pathological forms have been found 2,7 times less than in rats with experimental pathology.

These changes in spermogramm indices in rats coincide with literature data devoted to Tr pharmacological activity. Tr consists of *Tribulus terrestris* extract which contains steroid furostanol saponins. Due to its composition, this medicine is recommended for primary and secondary hypogonadism treatment, for men with infertility, erectile dysfunction and disturbances of reproductive function accompanied with oligo- and asthenospermia [17].

The using of Tr has caused normalization of spermatogonia number in the seminal channels and spermatogenesis index on the histological samples (see Table 1), which proved the most considerable effect of Tr that realized in the sperm cells motility increasing and, to a lesser extent, in their number and ejaculate volume [18].

The analysis of epididymal sperm cells' indices in rats with serotonin induced GP which were treated by cholecalciferol being a monotherapy (S + vit. D<sub>3</sub> group) has determined the statistically significant increasing by 2,2 of motile sperm percentage comparing with S group. At the same time, the morphological data of testicles' histological samples were more encouraging: number of normal spermatogonia in the channels and spermatogenesis index in this group of rats were significantly higher than the same indices in animals with GP. The correlation between vitamin D level and histological

structure of male sex glands in rats according to quantitative morphometric testicle indices has been shown in scientific work of Zamani A. et al. (2020) [19].

The introduction of D<sub>3</sub> vitamin together with Tr to rat males with experimental gonad damage has positively impacted all of spermogramm indices. Thus, the percentage of motile sperm cells has increased by 4,3 and their concentration has grown by 2 times, whereas pathological forms of sperm cells have been detected by 2,2 fewer comparing with S group rats.

During comparing animals which have received cholecalciferol at the time of therapy by referent medicine, the significant differences from last one haven't been observed (see Table 1).

However, other scientific investigations have reported vitamin D strong influence on sperm quality. It has been shown, vitamin D has positively connected with sperm cells motility and has had direct influence on sperms including nongenomic regulation of calcium intercellular homeostasis, activation of molecular ways which take part in sperm motility, and in capacitation and acrosome reaction [20]. The above listed determines vitamin D may positively influence on fertility in males. In addition, there are data about normal vitamin D level may be, probably, connected with higher possibility of getting pregnant and its better outcome [4].

Therefore, in addition to studying of vitamin D influence on spermogramm indices, the

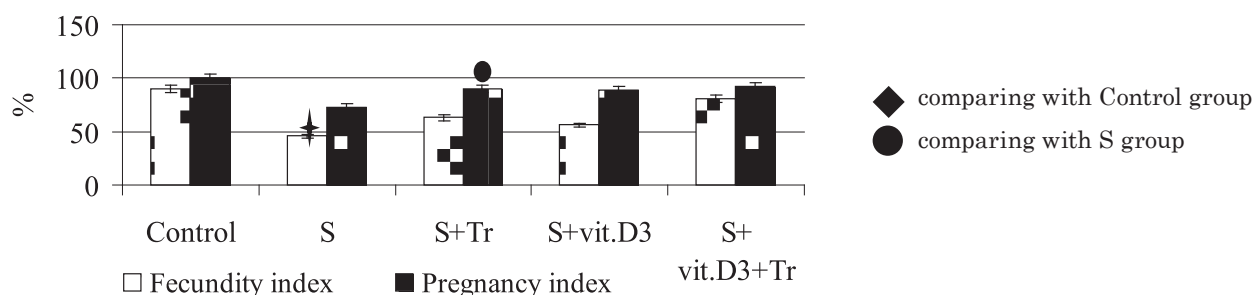


Fig. 2. Indices of males' fertility.

next part of this work was to research reproductive function of rats' males with GP which received cholecalciferol according to indicators of fertility and fecundity of females with normal estrus cycles fertilized by these experimental males.

It has been determined, that after three weeks, the males of experimental groups were able to fertilize females, although index of fecundity (fertility) has varied from 46 % (group S) to 90 % (control group) (Fig. 2). Meanwhile, there were slightly fewer pregnant females. Thus, the number of pregnant females was the smallest in S group — 73 % (100 % — in Control group of animals).

The decreasing of number of pregnant females fertilized by S group males, may be explained by embryonic deaths growing caused by defective sperm cells which were produced in testicles under the condition of serotonin induced ischemia [16] and have fertilized intact females.

The using of referent medicine or vitamin D to be a monotherapy haven't demonstrated positive effect according to indices of fertility calculated (see Fig. 2).

The correction of serotonin damage by simultaneous introduction of cholecalciferol and Tr (S + vit. D<sub>3</sub> + Tr group) has probably led to sperms quality improvement which resulted

in enlarged quantity of fertilized (81 %) and pregnant (92 %) females ( $p < 0,05$ ; in compare with pathology). Whereas, using of these medicines separately hasn't have the same effect (S + vit. D<sub>3</sub> and S + Tr groups) (see Fig. 2).

Embryonic deaths may be caused by mutagenic or nonmutagenic factors which resulted in fertilization problems (for instance, due to decreasing of normal and motile sperms number, disturbances of sperm cells' transport or capacitation — sperms penetration into egg) [21]. As a result, the changes of gonad metabolic processes which leads to deterioration of fertility or its fatal declining are observed; decreased number of fertilized females and substantial growing of embryonic deaths are detected. The same situation is, probably, observed under the condition of experimental GP.

Simultaneous using of vitamin D<sub>3</sub> and Tr in animals with serotonin-linked testicles damage (S + vit. D<sub>3</sub> + Tr group) has led to sperm cells quality improvement resulted in pregnancy development in the intact females fertilized by males from this group. Thus, the level of embryonic losses has declined close to the values of Control group' rats. The same result was detected in S + Tr group (Fig. 3).

This, in turn, has resulted in the number of alive fetuses in females fertilized by males with pathology and the ones who received medicines

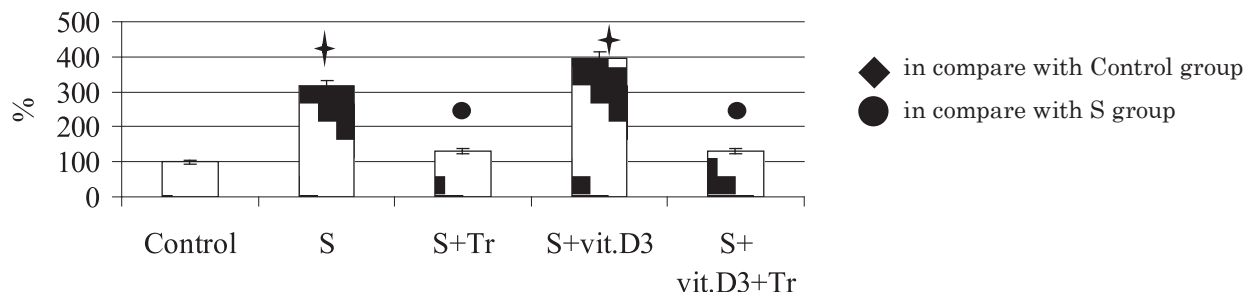


Fig. 3. The level of general embryonic losses in females fertilized by males with serotonin induced damage of testicles.

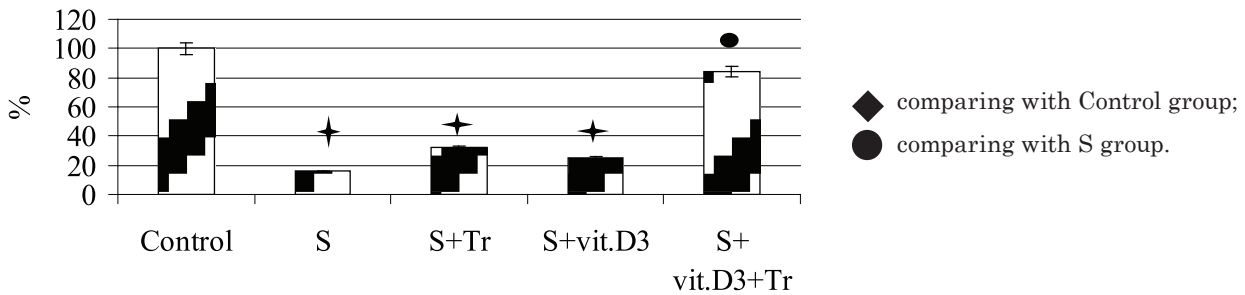


Fig. 4. Fecundity index (Fertility) (Fi).

for PG treatment. The average number of alive fetuses in S + vit. D<sub>3</sub> + Tr group has statistically exceeded the comparable figures in groups with GP as well as in those which received cholecalciferol or referent medicine.

The important indicator of parents' organism condition in animals with multifetal pregnancy is fecundity — the average number of alive fetuses per one female.

The exogenous and endogenous factors which change the hormonal status in the organism may influence fecundity. The estimation of fecundity and pregnancy results, in this case, ensures to evaluate the degree of reproductive system's damage in males [22]. According to data obtained in females which were mated with all experimental groups' males, except S + vit. D<sub>3</sub> + Tr group, the fecundity (fertility) index was declined due to decreasing of pregnant females' number as well as to embryonic losses growing.

Therefore, taking into consideration fecundity and fertility indices which determine the pattern of sexual behaviour described earlier [12] as well as quality of sperm, the Fi has been more than 6 times less in S group (experimen-

tal GP), 4 times less — in S + vit. D<sub>3</sub> and 3 times less — in S + Tr groups comparing with Control group ( $p < 0,05$ ). At the same time, this index was only by 16 percent fewer in S + vit. D<sub>3</sub> + Tr group comparing with Control (Fig. 4).

Thus, the using of vitamin D<sub>3</sub> or referent medicine as a monotherapy has led to improving of reproductive system' condition in animals with GP, however, the addition of cholecalciferol to base therapy of Tr has demonstrated better results than each of components separately.

Serotonin induced damage of testicles has led to declining of reproductive capacity of males, which has been expressed in decreasing of pregnant females' number and in the growing of general embryonic losses. The treating only by vitamin D<sub>3</sub> hasn't improved male reproductive system function resulted in decreased number of pregnant females matched with these males and in embryonic losses level. The correction by vitamin D<sub>3</sub> and Tr jointly has positively influenced the reproductive ability of males and recovered their fecundity and fertility.

## CONCLUSIONS

1. Under the condition of experimental serotonin-induced hypofunction of testicles, the disturbance of all indices of reproductive function has been observed: decreasing in sperm cells and motile sperms number, growing of pathological forms of sperms and declining of quantity of normal spermatogonia. The fertility indices have disturbed: the number of pregnant females was decreased and embryonic losses have grown; the integral index of realized fecundity has declined.
2. The introduction of cholecalciferol as a monotherapy during three weeks has led to sta-

tistically significant increasing of motile epididymal sperms quantity comparing with gonadopathy but has not reached intact animals' level; has normalized quantity of spermatogonia and index of spermatogenesis in seminal channels. The using of vitamin D<sub>3</sub> hasn't influenced general number and percentage of pathological sperms forms in rats' males with modelled testicles damage; hasn't improved males' reproductive function which has been resulted in declining number of pregnant females matched with them; embryonic losses have remained at the level of

- group of animals with serotonin induced gonadopathy.
- The introduction of vitamin D<sub>3</sub> together with Tribestan® to rats males with experimental serotonin induced damage of testicles has positively influenced all of spermogramm and morphometric indices. The significant effect on the fecundity has been observed: embryonic losses level has declined to Control group and quantity of alive fetuses has statistically exceeded the same index in group with pathology as well as in animals treated by cholecalciferol or referent medicine separately. The index of realized fecundity Fi has been normalized in rats received D<sub>3</sub> together with Tribestan®. Fi-index in this group of animals was higher than the same one in other experimental groups.
  - The using of cholecalciferol in complex schemes of treating of reproductive system disturbances due to gonads damage has led to improving of reproductive function and may be considered being pathogenetic therapy due to influence the different chains of reproductive health.

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ON THE REPRODUCTIVE SYSTEM FUNCTION IN RAT MALES  
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**Actuality.** Nowadays, the disturbances of men's reproductive function are the important problem which often accompany sex glands diseases. During last years, scientific researchers are taking into consideration vitamin D with aim to create safe medicines or treatment schemes for therapy hypofertility developed due to gonadopathies. It is thought, Vitamin D may improve not only spermogramm, but, probably, acts on men's reproductive ability by influencing fertility. The correction of reproductive disturbances requires the experimental grounding of vitamin D and its complex schemes using on the infertility experimental models.

**The aim** of this investigation was to determine the condition of rat males' reproductive system with experimental damage of testicles during correction by vitamin D<sub>3</sub>.

**Materials and methods.** The correction by vitamin D<sub>3</sub> (cholecalciferol) as a monotherapy or together with Tribestan® has been carried out in Vistar rats with experimental gonadopathy induced by Serotonin hydrochloride. The drug of comparison Tribestan® has been introduced *per os* in dose of 68 mg/kg body mass three days before Serotonin hydrochloride introduction; under the condition of serotonin obtaining (14 days) and during three days after its last injection once a day. Vitamin D<sub>3</sub> has been given according to the same scheme in value of 0,5 ml in dose of 4000 IU (*per os*). The male fertility has been determined according to fertility and fecundity indices of rats' females fertilized by experimental rats' males. Due to results of mating with intact females the integral index of average realized fecundity (fertility) of rats' males has been calculated. The researches of spermatogenesis have been carried out in epididymis's suspension; the morphometric indices were studied on the histological sections.

**Results.** Under the condition of serotonin induced gonadopathy the disturbance of all indices of fertility and reproductive function has been observed. The introduction of cholecalciferol as a monotherapy during three weeks has statistically increased the part of motile epididymal sperms relative to gonadopathy, but not reaching the intact animal's level; the number of spermatogonia and index of spermatogenesis have been normalized. However, the vitamin D using hasn't influenced general number and percentage of pathological forms of sperm cells in rats with modelled testicles damage; hasn't improve males' fertility. The introduction of vitamin D<sub>3</sub> together with Tribestan to rat mails with serotonin induced testicles damage has positively affected all the spermogramm and gonads morphometric indices. The fecundity, as an embryonic losses level, has almost declined to Control rats' values, whereas, the number of alive fetuses in thus group has been statistically higher than in groups with pathology as well as in those animals which obtained only cholecalciferol or referent medicine separately. The index of realized fecundity Fi has normalized in rats obtained vitamin D<sub>3</sub> together with Tribestan. Fi in this group was higher than in other experimental animals.

**Conclusions.** The using of cholecalciferol in complex schemes of treating of reproductive system disturbances due to gonads damage has led to improving of reproductive function and may be considered being pathogenetic therapy due to influence the different chains of reproductive health.

**Key words:** vitamin D, cholecalciferol, experimental gonadopathy, spermatogenesis, fertility.

ВПЛИВ ХОЛЕКАЛЬЦИФЕРОЛУ  
НА РЕПРОДУКТИВНУ ФУНКЦІЮ САМЦІВ ЩУРІВ  
ІЗ ЕКСПЕРИМЕНТАЛЬНОЮ ГОНАДОПАТІЄЮ

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**Актуальність.** Порушення відтворювальної здатності чоловіків є важливою проблемою сучасності і часто супроводжують захворювання статевих залоз. Для створення безпечних препаратів або розробки схем лікування гіпофертильності, що виникає внаслідок гонадопатій, останнім часом увагу дослідників привертає вітамін D, який може поліпшувати не тільки параметри спермограми, але є думки й про те, що він, можливо, діє на репродуктивний потенціал чоловіків, впливаючи на спроможність до запліднення. Корегування репродуктивних порушень потребує експериментального обґрунтування використання вітаміну D та комплексних схем його застосування на експериментальних моделях безпліддя.

**Метою** роботи було визначення стану репродуктивної функції самців щурів із експериментальною гонадопатією за умов корекції вітаміном D<sub>3</sub>.

**Матеріали та методи.** На щурах популяції Вістар із експериментальною гонадопатією, яку викликали введенням Серотоніну гідрохлориду, проводили корекцію за допомогою вітаміну D<sub>3</sub> (холекальциферолу) в якості монотерапії або разом із Трібестаном, який вводили *per os* в дозі 68 мг/кг маси тіла за три доби до початку введення Серотонін гідрохлориду, на тлі отримання серотоніну (14 діб) та протягом трьох діб після останньої ін'єкції серотоніну один раз на добу. Вітамін D<sub>3</sub> за тією ж схемою давали в об'ємі 0,5 мл в дозі 4000 МО (*per os*). Визначали фертильність самців за показниками фертильності та плідності самиць, запліднених дослідними щурами. За результатами паруння з інтактними самицями розраховувався інтегральний показник середньої реалізованої плідності. Досліджували сперматогенез у суспензії придатку сім'яника, а також вивчаючи морфометричні показники на гістологічних зрізах гонад.

**Результати.** При серотоніновій гонадопатії спостерігалось порушення всіх показників відтворювальної функції та показників фертильності. Введення холекальциферолу в якості «монотерапії» впродовж трьох тижнів вірогідно підвищувало частку рухливих епідидимальних сперміїв відносно гонадопатії, не досягаючи рівня інтактних тварин; нормалізувало кількість сперматогоніїв та індекс сперматогенезу у сім'яних каналцях. Однак, застосування вітаміну D<sub>3</sub> не впливало на загальну кількість і відсоток патологічних форм сперматозоїдів щурів зі змодельованим ураженням ячок; не покращувало відтворювальну здатність самців. Введення вітаміну D<sub>3</sub> сумісно з Трібестаном самцям щурів із експериментальним серотоніновим ураженням ячок позитивно впливало на всі показники спермограми та морфометричні показники гонад. Мала місце виражена дія на плідність, як на рівень внутрішньоутробних втрат, який знизився майже до значень щурів групи Контроль, так і на кількість живих плодів, яка статистично значуще перевищувала аналогічний показник у групах як із патологією, та тих, які приймали або тільки холекальциферол або референтний засіб окремо. У тварин, які отримували D<sub>3</sub> разом із Трібестаном, нормалізувався показник реалізованої плідності Фі, який був вищий за такий інших піддослідних груп.

**Висновки.** Використання холекальциферолу у комплексних схемах лікування порушень репродуктивної функції внаслідок або на тлі ураження гонад призводить до поліпшення стану відтворювальної здатності та є патогенетично обумовленим, бо впливає на різні ланки репродуктивного здоров'я.

Ключові слова: вітамін D, холекальциферол, експериментальна гонадопатія, сперматогенез, фертильність.