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CREATION OF MEDICINE FOR MALE STERILITY TREATMENT

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Male sterility is a body state wherein a man is not capable of impregnation. According to the research of different experts from 1 to 3 millions of couples out of 15 millions are sterile in Ukraine. Statistical data hereafter make it possible to evaluate the scale of the male sterility problem.

On WHO evidence 8-12% family couples in the whole world during all reproductive life run into the problem of sterility, and every year their number is increasing on a few million couples. For a long time it was considered that the birth of a child depended only on a woman, however presently, the half of sterile pairs' violations of reproductive function are revealed exactly from men [1, 19].

According to existent statistical information in the world, approximately 20% cases of infertility is conditioned only by a masculine factor, 50% because of woman's, and remaining 30% by complex infringement. Thus, pathology of spermatogenesis results to sterility in half cases [3] (fig.).

Today the problem of sterility in Ukraine is also sufficiently sharp for studying. Unfortunately, statistics are inexorable: 10% of women at the age of 18-44 years are sterile, 25% of women at the age of 18-44 have certain problems at the beginning of pregnancy; frequency of masculine factor in the general group of married couples with sterility makes about 50% [8].

Variety of factors, stipulating male sterility (MS), the complication of its development, functional intercommunication of male sexual glands with all systems and organs create large difficulties in development of adequate methods of spermatogenesis violations treatment.

Predominant reasons of MS are: varicocele, infection-inflammatory diseases of genital organs, patho-zoospermia, immunological violations, congenital anomalies, systemic diseases (tuberculosis, hepatitis, chronic kidney nephatony, inveterate diseases of respiratory organs, diabetes, epidemic parotitis, complicated with orchitis), surgical interferences concerning inguinal hernia, hidrocele, surgical interventions on an urinary bladder, sympathectomy, antitumour ray, hormone- and chemotherapy, application of some psycotropic agents, antihypertensive drug, antibiotics, sulfanilamides, nitrofurans, obstructive azoospermia, nek-rozoospermia, endocrine diseases and disorders. And

it is not a complete list of reasons of male sterility. It is necessary to mark that reason of MS can be regular toxicopathy, such as abuse of alcohol and nicotine, occupational hazards such as contact with organic and inorganic matters, influence of ionizing radiation, work in the conditions of high and low temperatures, long-lasting febricity with a temperature rise over 38°C, scrotum traumas, psychological traumas and other [7].

Poliaetiology of male sterility and variety of clinical aspects stipulate difficulties in its classification. Most clinicians distinguish:

- *secretory sterility* — at this form testicles do not produce enough number of sperm cells, necessary for achievement and impregnation of ovule, or at sperm mobility is broken, or majority of them have defects in a structure associated by intrinsic and acquired pathology;
- *obturative sterility* — at this form of sterility advancement of sperm cells in deferent ducts from one or both sides becomes impossible. At one-sided patency disorder there is a decline of sperm cells in sperm, at two-sided their complete absence;
- *complex infringement*, whenever secretory inefficiency of sexual glands combines with obstructive processes, immunological violations or inflammation;
- *immunological sterility* in 4-10% cases causes the development of autoimmune sterility at which against own sperm cells antibodies are produced [9]. Possibility of antibodies onset to sperms was studied more than 100 years ago by I.I.Mechnikov (1899) and R.Landsteiner (1899) and aligned with the presence on germ cells of new ideospecific antigens which are ignorant by the immunocompetent cells of organism;
- *relative sterility* is absence of some known reasons, in spite of careful examination of the married couples.

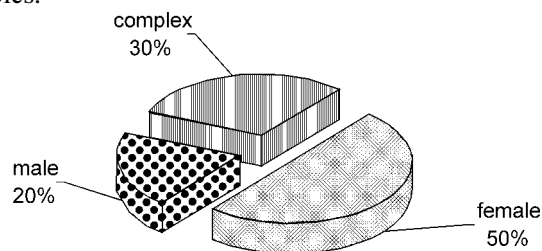


Fig. Statistical diagram of sterility factors.

There are works in which for comfort of orientation in reasons of masculine sterility in relation to the basic organ of the reproductive system — testicle — reasons are systematized as pretesticular (hypothalamus, hypophysis pathologies), testicular (varicocele, cryptorchidism, genetic factors) and post-testicular (arising up “difficulties” on the way of sperm cells advancement from testicles through deferent ducts into muliebrias).

According to data of different authors in 40-50% cases one of the most widespread reasons of sterility are post-testicular violations, such as: prostatitis, vesiculitis, erectile dysfunction.

Prostatitis (phlogistic prostate diseases) at the age of 50 years upward occupies the third place on frequency after innocent hyperplasia (adenoma) and prostate cancer [17]. There are different classifications of prostatitis, the great number of ambiguous concepts and terms are used in it.

However, presently the classification of prostatitis of the National institute of health of the USA (1995) is generally accepted, according to which there are four categories of prostatitis: I — acute prostatitis (acute infection of prostate gland) 5-10%, II — inveterate bacillary prostatitis (IBP, inveterate infection of prostate gland, characterized by recurrent infection of urinary tracks) — 8-35%, III — inveterate prostatitis/syndrome of inveterate pelvic pain 80-90% (III (a) is an phlogistic syndrome of inveterate pelvic pain, III (b) is a non-phlogistic syndrome of inveterate pelvic pain), IV — asymptomatic phlogistic prostatitis [11].

The prostatitis indicant of frequent occurrence is pain in a perineum (46% of patients), in a scrotum (39%), in an urinary bladder (6%), in a penis (6%), in lumbus (2%) and indicants of lower urinary tracks (hurried, painful urination and/or strangery) [6].

Prostatitis is very often succeeded by a vesiculitis (by inflammation of spermatocyst). The reason of disease can be a gonococcal infection or other microorganisms (colibacillus, staphylococcus, proteus) at a general virulent disease (influenza, angor, osteomyelitis) [14]. A vesiculitis is felt by sense of weight and pain in a perineum and rectum, increasing at urination and defecation, by abnormal pains at ejaculation, general weakness, apathy, temperature rise, by eliminations from an urethral channel and appearance of blood in sperm. One of the reasons resulting in MS is erectile dysfunction (ED) that is permanent inability to reach and/or support erection, necessary for satisfactory sexual activity [15].

Prevalence of ED among men of all ages, since the age of teenagers is 10-20%, thus amount of them is increasing every year, only in the countries of America and Europe average prevalence is 45% and increasing with age: from 30,8% in 30 years, to 76% by 70 [18]. There are:

- organic erectile dysfunction, in which vascular, neurogenic, hormonal and “cavernous” diseases are underlaid;

- psychogenic, when the medium suppression of erection mechanisms takes place in absence of organic reasons;
- mixed in combination of organic and psychogene changes.

Organic reasons, as a rule, are observed more than in 70-90% of cases, psychogene make less than 10%, but combination of those and other reasons takes place most often [2, 18].

Thus, poliaetiology of male sterility sets before itself the most difficult problem at the choice of certain tactic of treatment and doesn't allow to shorten the number of medicines used in therapy.

Treatment of MS is enough long process and efficiency of it depends on the age of man, amount and duration of diseases, resulting in the damage of spermatogenesis. Low efficiency of therapy is also conditioned by the lack of knowledge about the reproductive function of men, by absence of number of skilled urologists engaged in the problem of male sterility.

It should be remembered that treatment of violations of reproductive function of men without the proper examinations of patients is dangerous, because non grounded application of correcting or alternative hormonotherapy of people not having endocrine violations, can result in serious and proof violations of spermatogenesis.

Presently there are three categories of MS treatment: adjuvant reproductive methods, surgery, medicinal treatment.

Adjuvant reproductive therapy (ART) includes methods for the improvement of erectile dysfunction, induction of ejaculation, receipt of sperm and impregnation of ovule [5]:

- intracytoplasmatic sperm injection (ICSI) — a separate sperm cell is placed in the cytoplasm of mature ovule;
- partial zone dissection (PZD) — in two places damage is caused to pellucid zone (zona pellucida), using a sharp glass pipette; through these breaks sperm cells get into the ovule;
- subzonal injection (SUZI) — the selected sperm cells are injected in perivitelline space with the use of glass pipette.

Surgery at male sterility is conducted at obturation of spermaduct and varicosity. Widespread surgical diseases are varicocele, cryptorchidism, inguinal hernia, spermatocele, gidrocele et al weaken spermatogenesis and render negative influence on the reproductive function of man [4]. An operation on renewal of advancing ability of spermaduct is divided into 3 basic groups:

- vassal anastomosis (vasovasostomia; “vazo-” + grech. “stoma” — opening) is a surgical operation of imposition of anastomosis between the central and peripheral areas of spermaduct after excision of obliterated area;

Table 1

Medicines, used in therapy of male sterility

Pharmacological groups	Description of pharmaceuticals
Androgens:	
peroral	mesterolone (proviron), undecanoate of testosterone (andriol, testocaps)
parenteral	propionate of testosterone (testoviron), enantate of testosterone (testosterone-repository), testenat (sustanon-250), undecanoate of testosterone
transdermal	androderm, andractim, androgel
transcrotal	testoderm
hypodermic	implants of testosterone
Antiestrogens	Citrate of clomiphene (clostilbegid, tamoxifen)
Gonadotropins	anthropic menopausal gonadotropin (pergonal, menagon, khumegon), follitropins (metrodin, puregon), human chorionic gonadotropin (profazi, pregnil, khoragon)
Releasing hormones	lyuliberin, cryptokur
Inhibitors of prolactin secretion	Bromkriptin (parlodel), norprolakt, dostinex
Antimicrobial	Fluoroquinolones (ofloxacin, sparfloxacin, gatifloxacin, moksifloxacin), tetracyclines (doxycycline as a hydrochloride or maleate), macrolides (azithromycin, clarithromycin, spiramycin, dzhozamicin) and other
Immunostimulant	pyrogenal, normal human immunoglobulin, immunal, oktagam, viferon, neovir
Angioprotectors	pentoxifylline (trental, agapurin)
Enzymic preparations	vobenzim, flogenzim
Sexual function correction pharmaceuticals	yohimbe-hydrochloride, superyohimbe- plus, citrate of sildenafil (viagra), himkolin, carbegolin, alprostadil (edeks, kaverdzhekt), tentex, afrodor, imipramin, prozerin, atropine

- vassal epididymoanastomosis is an anastomosis of spermatiduct with the epididymis;
- vassal testicle anastomosis is an anastomosis of spermatiduct with tela of testicle.

In average, renewal of advancing ability for sperms after surgical treatment is succeeded in 20-30% of cases. Most effective is a surgery of anastomosis during all spermatiduct and renewal of its advancing ability for sperms makes 35-60%. Medicinal therapy at male sterility includes pharmaceuticals for the improvement of sperm generation, treatment of hormonal dysfunction and treatment of infections (table 1) [5].

It should be noted that possibilities of medicinal therapy at different violations, causing patospermia is

utterly limited that is the actual theme of clinical andrology.

On completion of the basic stage of the treatment stimulation of spermatogenesis is presented and to be exact for therapy in treatment it is necessary to add medicinal preparations (vitamin of E [10], carnitine, coenzyme Q 10 [12], leycopen, glutathione [12, 13, 16] and other) to the organism which will be actively instrumental in the process of formation of sperms, to strengthen blood providing of genital organs, improve the general state of patients. Numerous researches, conducted in Italy, Switzerland and other European countries have shown its high efficiency at male sterility.

Table 2

Assortment of home-produced medicines used for therapy of male sterility

Active substance	Pharmaceutical denomination	Manufacturer
Prostatilen	prostatilen, sup. 0,3 №5, 10	CJSC "Lechim-Kharkov"
	prostatilen-zinc, sup. №5, 10	CJSC "Lechim-Kharkov"
	prostatilen-biopharma amp.	OJSC "Biopharma"
Citrate of sildenafil	superviga 25, tab. of 25 mgs №1	JSC "Zdorov'e" company branch
	potenciale, tab. 0,1; 0,05 №1, 2	CJSC "Lechim-Kharkov"
	ergos, tab. of 0,025; 0,05 №2, 4	JSC "PharCoS" company branch
Hydrochloride of yohimbine	hydrochloride of yohimbine, caps. №50	JSC "Zdorov'e" company branch
	yohimbex-harmony, caps. №10	CJSC "Borchshagovskiy chimp harm zavod"
PHPS, pollen	Apiprost, caps. №10x6	JSC "Zdorov'e" company branch

Unfortunately, market of medicines of domestic production is presented by insignificant kinds of pharmaceuticals used at violations of the reproductive system for men and diseases (prostatitis, vesiculitis, erectile dysfunction and other) which are predominant reasons of this disease (table 2).

As you see from table 2, the market of pharmaceuticals of domestic manufacture is very limited and there is no enough reliable medicament which would provide complete recovery.

Therefore on the department of chemist's technology of drugs of the National University of Pharmacy (Kharkov) under the direction of the honoured worker of science of Ukraine, academician of Ukrainian AS, professor A.I.Tikhonov, the work on development of composition and technology of medicines of androgenic action is conducted. Original substances, becoming bases for the production of new apipreparations, presenting considerable interest and prospects of the

use in the different areas of pharmaceuticals, medicine, veterinary science and beekeeping were created.

It is known that preparations on the basis of products of beekeeping find active and wide application in modern medicine. Propolis, royal jelly, pollen, pollen load of a bee, bee venom possess the varied healthful properties, rendering antimicrobial, anaesthetic, antioxidant, anti-inflammatory, immunostimulating, reparative, antiradiational, antiviral, antitoxic, bracing actions.

It is necessary to mark that the special value at treatment of prostatitis, inveterate vesiculitis and erectile dysfunction which are predominant reasons of male sterility belongs to the pollen load of a bee, application of which get most bright and enough rapid effect in state improvement and normalization of MS sick.

From the above stated material, the problem of creation of complex medicinal preparation for treatment of various variants of masculine infertility gained the special medical and social meaningfulness.

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СОЗДАНИЕ ЛЕКАРСТВЕННОГО ПРЕПАРАТА ДЛЯ ЛЕЧЕНИЯ МУЖСКОГО БЕСПЛОДИЯ

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Бесплодие у мужчин — это состояние организма, при котором мужчина не способен к зачатию ребенка. Согласно исследованиям разных специалистов в Украине из 15 млн пар от 1 до 3 млн пар являются бесплодными. Изложенные ниже статистические данные позволяют оценить масштаб проблемы мужского бесплодия.

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СТВОРЕННЯ ЛІКАРСЬКОГО ПРЕПАРАТУ ДЛЯ ЛІКУВАННЯ ЧОЛОВІЧОГО БЕЗПЛІДДЯ

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Безпліддя у чоловіків — це стан організму, при якому чоловіки не здатні запліднювати яйцеклітину. Згідно з дослідженнями різних спеціалістів в Україні із 15 млн пар від 1 до 3 млн є безплідними. Викладені нижче статистичні дані дозволяють оцінити масштаб проблеми чоловічого безпліддя.