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TESTICULAR MICROLITHIASIS IN MALE INFERTILITY: PREVALENCE, DIAGNOSIS AND TREATMENT ALGORITHM

© *I.A. Korneyev [1, 2], R.D. Zasseev [2], A.A. Aloyan [1], A.A. Grinina [1], P.S. Kondrashkin [1], V.A. Makeev [1], V.E. Furin [1]*

[1] Academician I.P. Pavlov First Saint Petersburg State Medical University of the Ministry of Healthcare of the Russian Federation, Saint Petersburg, Russia;
[2] International Centre for Reproductive Medicine, Saint Petersburg, Russia

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Aim of study. To estimate testicular microlithiasis (TM) prevalence in men seeking help for infertility in reproductive medicine center, and generate an algorithm for TM management according to patient's choice to perform testicular biopsy or not. **Materials and methods.** We retrospectively reviewed charts of 143 consecutive adult male patients between 19 and 73 years (mean age 34.6 ± 7.9) seeking help for infertility in International Center for Reproductive Medicine. Gray-scale and color Doppler were used to calculate testicular volume and to study a spectrum of scrotal disorders including testicular microlithiasis. **Results.** Testicular size varied from 0.5 to 33.3 ml (mean 12.3 ± 5.8 ml), testicular hypoplasia, varicocele, hydrocele and epididymal cysts were detected in 88 (61.5%), 35 (24.5%), 9 (6.3%) and 50 (35%) patients respectively. TM signs were identified in 12 (8.4%) men, including 5 (42%) cases of classic TM and 7 (58%) cases of limited TM; 5 (42%) men had bilateral TM. One 1 (8%) patient with bilateral TM had ultrasonic appearance of non-palpable testicular tumor, radical surgical treatment was performed. Patients with TM had smaller testicles, higher prevalence of azoospermia and testicular tumor (p = 0.002, 0.013 and 0.085 respectively). All patients with TM were informed about their risks to harbor testicular cancer and taught self-examination technique. Testicular biopsy was offered to all men with concomitant risk factors for testicular cancer development, however none of the patients agreed. We have consequently developed algorithm for TM management according to patient's choice to perform or to avoid testicular biopsy. **Conclusion.** TM is common in infertile men, scrotum ultrasound is indicated to detect it. The suggested algorithm for TM management is aimed towards early testicular cancer detection and successful treatment with fertility potential preservation.

Keywords: testicular microlithiasis; male infertility; testicular cancer.

ТЕСТИКУЛЯРНЫЙ МИКРОЛИТИАЗ ПРИ МУЖСКОМ БЕСПЛОДИИ: РАСПРОСТРАНЕННОСТЬ, АЛГОРИТМ ДИАГНОСТИКИ И ЛЕЧЕНИЯ

© *И.А. Корнеев [1, 2], Р.Д. Зассеев [2], А.А. Алоян [1], А.А. Гринина [1], П.С. Кондрашкин [1], В.А. Макеев [1], В.Е. Фурин [1]*

[1] Федеральное государственное бюджетное образовательное учреждение высшего образования «Первый Санкт-Петербургский государственный медицинский университет им. академика И.П. Павлова» Министерства здравоохранения Российской Федерации, Санкт-Петербург;
[2] АО «Международный центр репродуктивной медицины», Санкт-Петербург

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Цель исследования. Изучение распространенности и структуры тестикулярного микролитиаза (ТМ) у мужчин, обратившихся в центр репродуктивной медицины, создание алгоритма ведения пациентов с ТМ. **Материалы и методы.** Проведен ретроспективный анализ обследования 143 мужчин (средний возраст — 34,6 ± 7,9 года), последовательно обратившихся в Международный центр репродуктивной медицины по поводу бесплодия. Обследование включало ультразвуковое исследование (УЗИ) органов мошонки, при котором оценивали их состояние и объем, регистрировали наличие и распространенность ТМ. **Результаты.** По данным УЗИ

объем яичек варьировал от 0,5 до 33,3 мл и в среднем составил 12,3 ± 5,8 мл, гипоплазия яичек, варикоцеле, гидроцеле и кисты придатков яичек были обнаружены у 88 (61,5 %), 35 (24,5 %), 9 (6,3 %) и 50 (35 %) пациентов соответственно. УЗ-признаки ТМ были выявлены у 12 (8,4 %) мужчин, классического, ограниченного и двустороннего ТМ — у 5 (42 %), 7 (58 %) и 5 (42 %) пациентов соответственно. У 1 (8 %) больного двусторонним ТМ были выявлены УЗ-признаки новообразования левого яичка, которое не было обнаружено при пальпации, проведено радикальное оперативное лечение. При наличии ТМ объем яичек был меньшим, азоospермию и новообразования яичек выявляли чаще, чем при отсутствии ТМ (p = 0,002, 0,013 и 0,085 соответственно). Пациентам с ТМ были даны разъяснения о необходимости проявлять онкологическую настороженность, выполнять рекомендации по самообследованию; мужчинам с имеющимися сопутствующими факторами риска развития рака яичка предложено выполнить биопсию яичек, однако ни один из обследованных пациентов согласие на это вмешательство не дал. Разработан алгоритм диагностики и лечения пациентов с ТМ с учетом их согласия на биопсию яичка или отказа от нее с целью минимизировать риск развития негативных последствий при отказе.
Заключение. ТМ распространен у бесплодных мужчин, с целью его выявления им показано проведение УЗИ органов мошонки. Предложенный алгоритм диагностики и лечения мужчин с ТМ нацелен на повышение вероятности раннего выявления злокачественных новообразований яичка и успешного лечения с сохранением перспектив реализации репродуктивной функции.

Ключевые слова: тестикулярный микролитиаз; мужское бесплодие; рак яичка.

INTRODUCTION

The widespread application of ultrasonography in clinical practice and the recommendation by professional communities to perform ultrasonography of the scrotum in case of male infertility [1, 2] contributed to an increase in patient referral for testicular microlithiasis (TM). Although microliths in testicular tissue were first described in the 20s of the last century [3, 4], the controversies in the incidence of TM, risks associated with TM, and management strategy for patients with different types of TM have not yet been resolved.

According to modern concepts, TM is defined as accumulation of calcium surrounded by layers of collagen fibers in the lumen of the seminiferous tubules or on the basal membrane of the seminiferous epithelium [5]. The reasons for the formation of the microlith nucleus are completely unclear. Microliths are suggested to form during desquamation of seminiferous epithelium, as a result of the excessive activity of the Sertoli cells, or disposal of abnormally located cells during testicular dysgenesis. The surrounding structures are gradually involved in the mineralization of the nucleus; therefore, over time, the size of the microlith increases, and this can lead to the impaired patency and expansion of the seminiferous tubules [6]. These processes can sometimes provoke the development of scrotal pain [7], but TM is usually asymptomatic and determined by ultrasonography of the testicles, which is performed due to the changes in size and consistency of the testicles or marital infertility [8].

The prevalence of TM is controversial: a comparative analysis of research data showed variability and differences in the results, while TM appeared to be more common in men with scrotum-associated symptoms than in asymptomatic men, that is, 8.7%–18.1% and 0.6%–9%, respectively [9].

TM are suspected to include both congenital and acquired factors. The risk of this condition is 2.17-fold higher in men of African than in men of European descent. Microliths can be formed simultaneously in the organs of the reproductive, respiratory, and nervous systems, which may be due to genetic defects that have not yet been established. TM seemed to occur more often in physically less active and socially disadvantaged men, as well as among those with large consumption of potato chips and popcorn [10, 11]. TM is commonly associated with other diseases including cryptorchidism, hypogonadism, testicular torsion, varicocele, hydrocele, spermatocele, as well as non-Hodgkin's lymphomas, cystic fibrosis, and Klinefelter and Down syndromes [3, 12, 13]. An analysis of 17 publications also showed a decrease in fertility in TM, which suggests the relationship between TM and testicular dysgenesis syndrome [11]. In addition, many researchers have confirmed a higher risk of testicular cancer in men with TM: a meta-analysis of published works reported more than 12-fold increase [14–16].

Despite the fact that microliths do not contain tumor elements, the findings of Russian and foreign specialists allow us to consider TM as a precancerous condition and to provide oncological warnings in TM. Indeed, according to the European Association of Urology, physicians should advise patients with TM to regularly perform self-testicular examination, and in the presence of risk factors for tes-

ticular cancer, which include infertility and bilateral TM, testicular hypoplasia (testicular volume less than 12 ml), cryptorchidism, previously identified testicular cancer and contralateral TM, they should offer testicular biopsy for early detection of malignant lesion (defined as high-grade recommendation) [2].

Typical sonographic features of TM are 1–3 mm uni- or bilateral, hyper-echoic testicular foci with slight or no acoustic shadows, and it was proved to have high reproducibility in ultrasound measurements carried out by different individuals or by the same researcher [17]. According to the number of microliths detected by ultrasonography, several definitions and classification systems for TM were proposed [18]. However, two categories of TM, proposed by Bennett et al. [19] in 2001, were most widely used, that is, classic (detection of ≥5 microliths in the testicle within the same ultrasound scan), and limited (detection of a smaller number of microliths). The clinical and prognostic value of these categories has not been finally determined, but most experts agree that the formation of a cluster – accumulations of microliths – may indicate a dysgenesis site in which the probability of detection of testicular carcinoma *in situ* is high [20].

To date, discussions continue about what should be the algorithm for managing men with TM. There are controversies in research conclusions and recommendations of professional communities [21, 22], which impede standardization of approaches. In this regard and considering the small number of publications on TM in the Russian literature and the unwillingness of Russian patients with TM to comply with the recommendations proposed by the European Association of Urology, we decided to perform this study.

The aim of the study was to investigate the incidence and structure of TM in men who referred to the center of reproductive medicine for treatment of marital infertility. We also aimed to develop an algorithm for the management of men with TM, which will determine the doctor's action plan depending on the availability of clinical data and take into account the possibility of patient refusing a testicular biopsy.

MATERIALS AND METHODS

Diagnostic findings of 143 men aged 19–73 years, (mean age, 34.6 ± 7.9) who consecutively referred to the international center of reproductive medicine for marital infertility, were retrospectively analyzed. Medical history taking, clinical examination, and laboratory and instrumental tests were performed according to clinical recommendations, and the quality of semen analysis was assured by adherence to the World Health Organization 2010 Laboratory Manual [23]. All patients underwent scrotal ultrasonography using an ultrasound machine Clear View 550 (Philips, Netherlands) with 4–12 MHz broadband linear probes in grayscale and color Doppler imaging modes. During scanning, images of testicles and their shells, epididymides, and components of vas deferens were obtained; microlithiasis, its extent, and signs of other conditions were registered; and testicular size was measured in three mutually perpendicular planes. The volume of each testicle was calculated by the product of the obtained values and coefficient 0.7. Color Doppler ultrasound was used to determine the degree of vascularization in the regions of interest.

Obtained results were processed using SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA), and mean of variables are indicated with standard deviation ($m \pm SD$). Chi-square test, Fisher exact test, and t-test were used to evaluate difference between groups. The level of significance was set as $p \leq 0.05$.

RESULTS

The history of disease showed that the spouses had unsuccessful attempts to become pregnant naturally from 1 to 18 (mean time, 2.5 ± 0.3) years. Before referral to the center, 21 (14.7%) men underwent surgery: 9 (43%) for inguinal cryptorchidism, of which 3 (33%) had unilateral and 6 (66%) had bilateral cryptorchidism; 7 (33%) for varicocele and hydrocele, with 7 (33%) and 2 (10%) patients, respectively; 2 (10%) for bilateral testicular biopsy for azoospermia; and 1 (5%) for bilateral vasectomy. Three (2.1%) patients reported a history of unilateral orchoepididymitis.

In the semen analyses, azoospermia, oligozoospermia, asthenozoospermia, and teratozoospermia were detected in 28 (19.6%), 44 (30.8%), 42 (29.4%), and 70 (49%) men, respectively. A hormone profile indicated hypergonadotropic hypogonadism in 13 (9.1%) patients.

On scrotal ultrasonography, the volume of testicles ranged from 0.5 mL to 33.3 mL (mean volume, 12.3 ± 5.8 mL). Sonographic measurements were

normal in 29 (20.3%) patients, testicular hypoplasia (volume <12 mL) was detected in 88 (61.5%) men, of which 50 (57%) had bilateral, 18 (21%) had left-sided, and 20 (23%) had right-sided hypoplasia. Sonographic features of varicocele were found in 35 (24.5%) patients, of which 33 (94%) had them on the left side only and 2 (6%) had them on both sides. Unilateral hydrocele was found in 9 (6.3%) patients, predominately left-sided in 7 (78%) men. Epididymal cysts were found in 50 (35%) patients, 10 (20%) of them had bilateral and 25 (50%) and 15 (30%) were right-sided and left-sided epididymal cysts, respectively.

Sonographic features typical for TM were observed in 12 (8.4%) men; 5 (42%) of them met the criteria of classic type and 7 (58%) of limited type TM. Bilateral TM was found in 5 (42%) patients, while the rest had microliths on one side only, with 3 (25%) on the left and 4 (33%) on the right. One (8%) patient with bilateral TM had sonographic signs of tumor in the left testicle, which was not found during palpation. Results of clinical and laboratory examination of men are represented in the table: the testicular volume was lower and the azoospermia was detected more often in the TM group (t = 3.54; p = 0.002 and 0.013, respectively). No significant differences were found in other variables the between groups; however, the TM group tended to have higher frequency of tumors (p = 0,085).

A man with sonographic signs of testicular neoplasm (Fig. 1) was admitted to the oncourology department. A left orchifuniculectomy was performed, and the histological examination of the specimen showed a mixed germ cell tumor of the left testicle represented by seminoma and mature postpubertal teratoma with intratubular germ cell neoplasia (pT1).

All other patients with TM received explanations on the need to be on cancer alert and follow the recommendations for testicular self-examination and treatment, taking into account the risk factors for testicular malignancy. Indeed, bilateral testicular biopsy was recommended to patients with signs of testicular deficiency and bilateral TM and TM associated with testicular hypoplasia, or history of cryptorchidism due to high risk of carcinoma *in situ*, but none of the examined patients gave consent for this intervention. Hence, an enlightening talk was given, annual scrotal ultrasonography with urologist consultation was suggested, and regular testicular self-examination was recommended in between. For pathological signs, including changes in the size, shape, or consistency of the testicles, an urgent referral to specialist to clarify the diagnosis and receive treatment as soon as possible was advised.

Clinical parameters in patients with and without testicular microlithasis (*m* ± *SD*)
Распределение результатов обследования мужчин в зависимости от наличия ТМ (*m* ± *SD*)

Parameter	TM(+) (n = 12)	TM(–) (n = 131)	All patients (n = 143)
Age of men, years	33.3 ± 3.4	34.7 ± 8.2	34.6 ± 7.9
Mean volume of testicles, mL	7.7 ± 4.7	11.7 ± 6.1*	12.3 ± 5.8
Testicular hypoplasia	10 (83 %)	78 (60 %)	88 (61.5 %)
Epidydimal cysts	3 (25 %)	47 (35.7 %)	50 (35 %)
Varicocele	4 (33 %)	31 (24 %)	35 (24.5 %)
Hypergonadotropic hypogonadism	1 (8 %)	12 (10.1 %)	13 (9.1 %)
Hydrocele	0 (0 %)	9 (6.9 %)	9 (6.3 %)
Testicular cancer	1 (8 %)	–	1 (0.7 %)
Azoospermia	6 (50 %)	22 (16.8 %)*	28 (19.6 %)
Oligozoospermia	3 (25 %)	41 (31.3 %)	44 (30.8 %)
Asthenozoospermia	4 (33 %)	38 (29 %)	42 (29.4 %)
Teratozoospermia	4 (33 %)	66 (50.4 %)	70 (49 %)

Note. TM (+), presence of testicular microlithiasis; TM(–), absence of testicular microlithiasis. * p < 0,05.

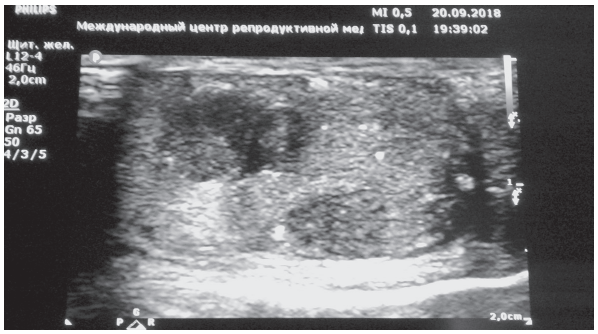

Fig. 1. Ultrasonic scan of left testicle in patient with bilateral testicular microlithiasis with echo structural heterogeneity typical for testicular neoplasm

Рис. 1. Ультразвуковое исследование левого яичка у мужчины с билатеральным тестикулярным микролитиазом. Определяются множественные микролиты и неоднородность эхоструктуры, характерная для новообразований яичка

DISCUSSION

This study gave data on the incidence and structure of TM in men among infertile couples, with an incidence rate of 8.4%, which corresponds with the results of other similar investigations [24, 25]. However, compared with the study by Yee et al. [25], limited type TM was more common than the classic type, and this was probably caused by individual specifics or difference in requirements for ultrasound protocol in different medical institutions.

Generally, our results confirm the current understanding of the relationship between TM and testicular dysgenesis syndrome [16]: men with microliths had more frequent azoospermia and smaller testicles. Moreover, the fact that a single patient who had testicular neoplasm detected by ultrasonography also had a bilateral TM supports the position to consider this disease as a precancerous condition, for which testicular biopsy is recommended in patients with risk factors and testicular self-examination is advised in patients with no risk factors [21]. Given the low compliance by examined men to the recommendation of testicular biopsy, we developed an algorithm of diagnosis and treatment of patients with TM (Fig. 2), which allows minimizing the risk of adverse outcomes from refusal to testicular biopsy.

According to this algorithm, men with TM who had risk factors (bilateral TM, male infertility associated with impaired spermatogenesis, testicular hypoplasia, cryptorchidism, history of surgery for cryptorchidism, or testicular neoplasm) should be informed about the high risk of clinically occult testicular cancer (carcinoma *in situ*), and testicular biopsy should be recommended for its exclusion or confirmation. If testicular cancer is confirmed, oncourologic care is indicated. Patients should be informed on the methods of semen cryopreservation, offering sparing reproductive function realization. Men who refused testicular biopsy should be informed about assumed risks, which may be decreased by having annual scrotal ultrasonography with urologist consultation and regular testicular self-examination in between. To enhance compliance with the recommendations, reporting the effect of the delay in the diagnosis at the prehospital stage on the treatment results is necessary [26] in patients with testicular tumors. As men older than 50 years have markedly reduced risk of developing testicular neoplasms, they can be allowed to refuse annual visits to specialists, while maintaining regular testicular self-examination. The final recommendation is addressed to patients in whom a testicular biopsy did not reveal a testicular neoplasm.

Since testicular self-examination plays a crucial role in early detection of malignant transformation in the testis, the patient should be trained to correctly perform it. In our experience, the materials of the website of the European Association of Urologists, prepared to inform patients, substantially help in explaining the technique for such an examination and in consolidating the acquired practical skills.

Analysis of our results also demonstrates the incidence of male infertility factor in marriage and the high rate of scrotal pathology in infertile men, which confirms the appropriateness of ultrasonography in this population. Sonographic features of both testicular hypoplasia and previous or ongoing pathological processes were found in many patients. The frequency of epididymal cysts in our patients corresponded with those in foreign reports, and hydrocele and varicocele were more common [27–29]. Furthermore, similar to other specialists, we did not

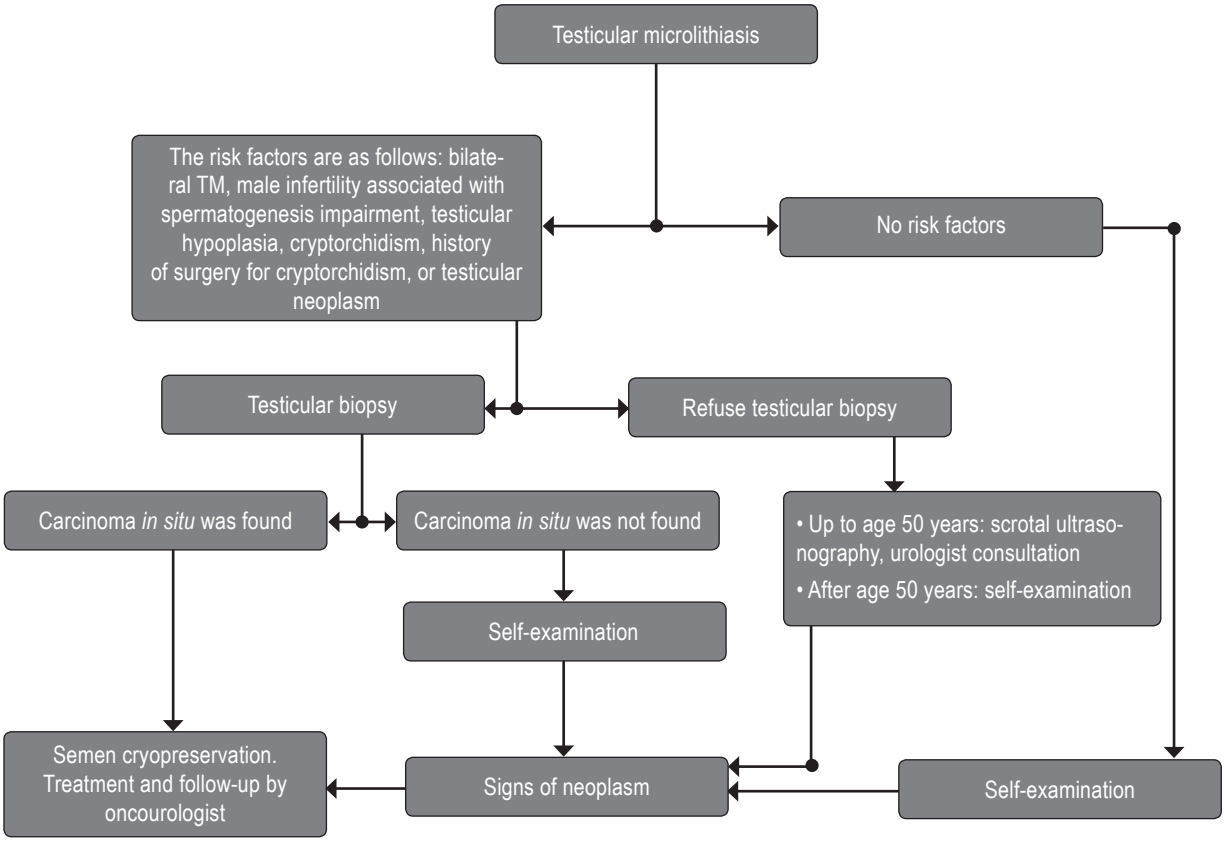

Fig. 2. Algorithm for diagnosis and treatment of patients with testicular microlithasis
Рис. 2. Алгоритм диагностики и лечения пациентов с тестикулярным микролитиазом

find significant difference in TM incidence in men with these conditions.

Additionally, despite the binding regulatory acts of the Ministry of Health of the Russian Federation, which recommends examination at 3–6 months to identify the causes of male and female infertility, to treat them for 9–12 months if appropriate indications are identified, and to send them for treatment using assisted reproductive technologies in the absence of pregnancy, we found that many patients referred to our International Center for Reproductive Medicine much later. It appears clear that urologists, obstetrician-gynecologists, and general practitioners should continue to educate the public and other medical professionals, emphasizing the importance of a woman's age and the length of the infertility period among the factors determining the success of treatment.

CONCLUSION

Thus, our study confirms the current state of the high prevalence of TM in infertile men, the appropriateness of scrotal ultrasonography for male infertility to detect TM and, if detected, the need to be aware of cancer risk. Our algorithm of diagnosis and treatment of men with TM consistent with expectations of Russian patients is aimed at increasing the likelihood of early detection of testicular malignancies and successful treatment while maintaining the prospects for reproductive function.

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Information about the authors:

Igor A. Korneyev — Doctor of Medical Science, Professor, Department of Urology, Academician I.P. Pavlov First Saint Petersburg State Medical University of the Ministry of Healthcare of the Russian Federation; Medical Director, International Centre for Reproductive Medicine, Saint Petersburg, Russia. SPIN: 4780-2266. E-mail: iakorneyev@yandex.ru.

Ruslan D. Zasseev — Urologist, International Centre for Reproductive Medicine, Saint-Petersburg, Russia. E-mail: r.zasseev@gmail.com.

Aram A. Aloyan — Student, Academician I.P. Pavlov First Saint Petersburg State Medical University of the Ministry of Healthcare of the Russian Federation, Saint Petersburg, Russia.

Anastasia A. Grinina — Student, Academician I.P. Pavlov First Saint Petersburg State Medical University of the Ministry of Healthcare of the Russian Federation, Saint Petersburg, Russia.

Pavel S. Kondrashkin — Student, Academician I.P. Pavlov First Saint Petersburg State Medical University of the Ministry of Healthcare of the Russian Federation, Saint Petersburg, Russia.

Vladimir A. Makeev — Student, Academician I.P. Pavlov First Saint Petersburg State Medical University of the Ministry of Healthcare of the Russian Federation, Saint Petersburg, Russia.

Valeriy E. Furin — Student, Academician I.P. Pavlov First Saint Petersburg State Medical University of the Ministry of Healthcare of the Russian Federation, Saint Petersburg, Russia.

Сведения об авторах:

Игорь Алексеевич Корнеев — д-р мед. наук, профессор кафедры урологии. ФГБОУ ВО ПСПбГМУ им. акад. И.П. Павлова Минздрава РФ, Санкт-Петербург; медицинский директор АО «Международный центр репродуктивной медицины», Санкт-Петербург. SPIN: 4780-2266. E-mail: iakorneyev@yandex.ru.

Руслан Дзамболатович Зассеев — врач-уролог. АО «Международный центр репродуктивной медицины», Санкт-Петербург. E-mail: r.zasseev@gmail.com.

Арам Ашотович Алоян — студент. ФГБОУ ВО ПСПбГМУ им. акад. И.П. Павлова Минздрава РФ, Санкт-Петербург.

Анастасия Анатольевна Гринина — студент. ФГБОУ ВО ПСПбГМУ им. акад. И.П. Павлова Минздрава РФ, Санкт-Петербург.

Павел Сергеевич Кондрашкин — студент. ФГБОУ ВО ПСПбГМУ им. акад. И.П. Павлова Минздрава РФ, Санкт-Петербург.

Владимир Александрович Макеев — студент. ФГБОУ ВО ПСПбГМУ им. акад. И.П. Павлова Минздрава РФ, Санкт-Петербург.

Валерий Евгеньевич Фурин — студент. ФГБОУ ВО ПСПбГМУ им. акад. И.П. Павлова Минздрава РФ, Санкт-Петербург.