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Results of program used for intracytoplasmic sperm injection in in-vitro fertilization

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The work presents the analysis of the effective method for intracystoplasmic sperm injection (ICSI) in the extra corporal fertilization. The study included 180 couples with male infertility factor who had received medical aid in the Institute of Reproductive Medicine (Kyiv) during 2013–2015. The diagnoses were verified, the patients were examined in accordance with the clinical protocols. The ICSI procedure was performed by the common methods. Before the start, the women underwent the course of controlled ovarian stimulation according to the well known classic protocol.
The received data were considered taking into account the type of pathospermia (oligoasthenozoospermia, obstructive and non-obstructive azoospermia). As a result of two cycles, the biochemical pregnancy was noted in 97 out of 180 couples (53.9%). But, after the reproductive losses which were the highest between men with non-obstructive azoospermia (14.3% versus 4.5%), the child birth reached 92 (51.1±3.7%), along with group with oligoasthenozoospermia – in 65 out of 120 (54.2±4.5%), obstructive azoospermia in 21 out of 38 (55.3±7.5%), non-obstructive – in 6 out of 22 (27.3±9.0%) the last value was statistically less.
This information testifies to the necessity to look for the elevation of the ICSI effectiveness. Nowadays, the most actual in this aspect is considered the improvement of selection criteria for including into the program, with this – the decisive importance belongs to the study of risk factors spectrum which would assure the personified approach to solve the problem.
Key words: *male infertility, ICSI program, results.*

Результаты применения программы интрацитоплазматической инъекции сперматозоида при оплодотворении in-vitro

Ю.Н. Гурженко, А.О. Куценко

В роботе приведен анализ эффективности методики интрацитоплазматической инъекции сперматозоида (ICSI) при проведении оплодотворения in-vitro. Объем исследования представлен 180 парами с мужским фактором бесплодия, которым была оказана медицинская помощь на базе Института репродуктивной медицины (Киев) в 2013–2015 годах. Диагнозы верифицированы, пациенты обследованы в соответствии с клиническими протоколами. Процедура ICSI проведена за общепринятой методикой. Женщины перед началом программы прошли курс стимуляции суперовуляции согласно известным классическим протоколам.
Полученные данные рассматривались с учетом вида патоспермии (олигоастенозооспермия, обструктивная и необструктивная азооспермия). В результате двух циклов биохимическая беременность настала у 97 из 180 пар (53,9%). Однако после репродуктивных потерь, которые были наибольшими среди мужчин с необструктивной азооспермией (14,3% против 4,5%), рождение ребенка достигнуто у 92 (51,1±3,7%). При этом в группе с олигоастенозооспермией у 65 из 120 (54,2±4,5%), обструктивной азооспермией – у 21 из 38 (55,3±7,5), необструктивной – у 6 из 22 (27,3±9,0%) последняя величина достоверно меньше.
Приведенная информация свидетельствует о необходимости поиска путей повышения результативности ICSI. На сегодня наиболее актуальным в этом аспекте представляется усовершенствование критериев отбора для включения в программу. При этом решающее значение приобретает изучение широкого спектра факторов риска, овладение которыми обеспечит персонифицированный подход решения вопроса.
Ключевые слова: *мужское бесплодие, программа ICSI, результаты.*

Результати застосування програми інтрацитоплазматичної ін'єкції сперматозоїда при заплідненні in-vitro

Ю.М. Гурженко, А.О. Куценко

У статті наведено аналіз ефективності методики інтрацитоплазматичної ін'єкції сперматозоїда (ICSI) при проведенні запліднення in-vitro. Обсяг дослідження представлений 180 парами з чоловічим фактором безплідності, яким була надана медична допомога на базі Інституту репродуктивної медицини (Київ) у 2013–2015 роках. Діагнози верифіковані, пацієнти обстежені відповідно до клінічних протоколів. Процедура ICSI проведена за загальноприйнятою методикою. Жінки перед початком програми пройшли курс стимуляції суперовуляції згідно з відомими класичними протоколами.
Отримані дані розглядалися з урахуванням виду патоспермії (олігоастенозооспермія, обструктивна і необструктивна азооспермія). У результаті двох циклів біохімічна вагітність настала у 97 з 180 пар (53,9%). Однак після репродуктивних втрат, які були Найбільшими серед чоловіків з необструктивною азооспермією (14,3% проти 4,5%), народження дитини досягнуто у 92 (51,1±3,7%). При цьому у групі з олігоастенозооспермією у 65 з 120 (54,2±4,5%), обструктивною азооспермією – у 21 з 38 (55,3±7,5), необструктивною – у 6 з 22 (27,3±9,0%) остання величина достовірно менше.
Наведена інформація свідчить про необхідність пошуку шляхів підвищення результативності ICSI. На сьогодні найбільш актуальним у цьому аспекті видається удосконалення критеріїв відбору для включення у програму. При цьому вирішальне значення набуває вивчення широкого спектра чинників ризику, володіння якими забезпечить персоніфікований підхід вирішення питання.
Ключові слова: *чоловіча безплідність, програма ICSI, результати.*

The challenge of overcoming the declining trend in the population, its reproduction, which exists in Ukraine and is caused by well-known reasons, is the prerogative of the state. The healthcare industry remains an important aspect in the implementation of policies aimed at preservation of public health, life span and quality. The birth rate and mortality are among the most important and sensitive indicators of the demographic situation. With the low level of the first indicator and high level of the second one, a correlation is created regarding the real threat to society's security, the development of its labor potential [3]. Hence, the aspect of this problem such as reproductive health becomes particularly relevant [8]. The infertility, as a result of a violation of its condition, is a serious, difficult issue that concerns almost all spheres of life. The world statistics testifies to frequent infertil-

Table 1

The age distribution of partners in married couples included in the ICSI IVF program in cases of male infertility

Age	Men			Women		
	Abs.	%	m	Abs.	%	m
Aged under 24 years	28	15,6	2,7	21	11,7*	2,1
20–29	47	26,1	3,2	51	28,3	3,1
30–34	53	29,4	3,4	57	31,7	3,2
35–39	24	13,3	2,5	41	22,8*	3,2
40–44	19	10,6	2,3	10	5,5	1,6
≥45	9	5,0	1,6	-	-	-
	180	100,0		180	100,0	

Note: * – the difference between the indicators in the line is reliable; $p<0.05$.

Table 2

The source data of follicular and ovarian phases after one cycle of stimulation of superovulation of women from pairs with male infertility, included in the ICSI program (n = 180)

Parameters	Types of pathospermia		
	Oligoasthenozoospermia, n=120	Obstructive azoospermia, n=38	Non-obstructive azoospermia, n=22
Follicles: M±m	11,6±0,4	10,9±0,5	12,1±0,3
Obtained oocytes: M±m	10,0±0,5	9,2±0,3	9,9±0,6
Mature oocytes: M±m %, m	8,2±0,2* 82,0±3,5	7,7±0,5 83,7±4,5	7,7±0,2 77,7±3,5
Immature oocytes: M±m %, m	1,4±0,3 14,0±2,0	1,2±0,2 13,0±3,4	1,8±0,3 17,2±2,6
Degenerated oocytes: M±m %, m	0,4±0,1 4,0±1,5	0,3±0,3 3,3±1,2	0,4±0,1 4,0±1,8

Note: * – the difference between the values of the first and third indicators in line is reliable; $p<0,05$.

ity and the growth of human factor share over the years [1, 5]. The situation in Ukraine is similar. According to various sources, about 1 to 3 million partner couples have difficulties with childbirth. According to the official statistics, there were 40,274 cases of female infertility and 1,249 male infertility in 2015 [8, 9].

The difficulties of the socioeconomic, environmental, and even political nature that are observed in Ukraine have a negative impact on male fertility, as manifested in certain tendency to decline in the sperm quality [7, 11]. The presence of a variety of risk factors for male infertility complicates its topical diagnosis and treatment, the traditional approaches to which often fail. With the development and achievements of science, there are dynamic changes in the principles of assistance to the contingent of infertile men [15, 18]. New assisted reproductive technologies (ART) are introduced into clinical practice and begin to acquire a leading position in the structure of treatment methods [2, 6, 12].

The intracytoplasmic sperm injection (ICSI) method, as one of the ART techniques, is included into the most common and effective methods for restoring fertility in infertile couples with male infertility [4, 14]. According to the literature, the application of several program attempts makes it possible to achieve the desired pregnancy in the end result in 50–60% of cases [17]. At the same time, the number of publications on this issue is limited. A broad discussion of the accumulated information on the provision of such assistance will enable its critical assessment in order to identify ways to improve quality [4, 16]. The foregoing stipulated the purpose of the study: to analyze the effectiveness of the intracytoplasmic sperm injection (ICSI) method in case of ART.

MATERIALS AND METHODS OF STUDY

The work was performed under the auspices of Institute of Reproductive Medicine (IRM), Kyiv. The study period is 2013–2015. The object of study was 180 married couples, when the procedure for fertilization was carried out using the method of intracytoplasmic sperm injection into oocyte cytoplasm (ICSI). The primary document was out-patient medical records adapted to the study tasks (file No. 22/0). The results of complex clinical and laboratory examination and treatment carried out in accordance with existing clinical protocols were analyzed. The diagnoses were verified on their basis, and it was confirmed that women were apparently healthy. The criteria for inclusion into the study are as follows: sexual and ejaculatory functions are not disordered; regular sexual life with a certain frequency during the last year or longer; the married couple has no acute infectious and inflammatory diseases, oncological pathology and, if necessary, the treatment of concomitant diseases is completed; absence of conservative infertility treatment during 6 months. The age distribution of partners of a married couple is presented in the Table 1.

The results of analysis of the Table 1 indicate that the number of men aged under 30 years and 30–39 years old was the same (41.7±3.6% and 42.7±3.6% respectively). Against such a backdrop, the age difference of women stands out. In the second period, there were significantly more than in the first one (54.4±3.6% vs. 40.0±3.4%, respectively). The percentage of the men aged 40 and older significantly exceeded: 15.6±2.7%, while women – 5.5±1.6% ($p<0.05$).

In cases of azoospermia, the testes biopsy (TSE), aspiration and biopsy of them or epididymis (TESA, RESA) were performed. We emphasize that all women underwent a course of controlled ovarian stimulation (COS) in accordance with classical, well-known protocols. In order to determine the response of the ovaries, the estradiol level was monitored and ultrasound monitoring was performed as to the growth of the follicles every 2–3 days. In statistical processing of the obtained data, the aver-

Table 3

Key indicators of the early stage of embryogenesis, taking into account the type of pathospermia in men in the ICSI program

Parameters	Types of pathospermia		
	Oligoasthenozoospermia, n=120	Obstructive azoospermia, n=38	Non-obstructive azoospermia, n=22
Fertilized oocytes (metaphase II); M±m	6,4±0,3*	5,8±0,1*	4,0±0,2*
Absence of fertilization; M±m %, m	1,8±0,1 22,0±2,4	1,9±0,2 24,6±4,5	3,7±0,3* 48,0±4,1
Zygotes per 24 hours: M±m, %, m	5,0±0,3 78,1±2,3	4,4±0,4 75,9±2,1	3,1±0,5* 77,5±1,9
Number of embryos at the stage of 48 hours; M±m, %, m	4,5±0,2 90,0±1,7	3,9±0,4 88,4±3,3	2,6±0,5* 83,8±5,0
Absence of fission; M±m, %, m	1,4±0,4 21,9±2,5	1,4±0,5 23,2±1,9	0,9±0,4 22,5±2,1
Number of embryos at the stage of 72 hours; M±m, %, m	3,8±0,1 85,0±4,4	3,1±0,2 79,5±5,0	1,7±0,1 65,4±6,1*
Blastulation at the stage of 120 hours; M±m,	3,6±0,2*	2,8±0,1*	1,2±0,4*

Note: * – the difference between the indicators in the line is reliable; p <0.05.

age values, the average error and Student's T-Test criterion with the confidence level of 0.95 for assessment of the significance of differences in values were calculated.

RESULTS AND THEIR DISCUSSION

The core component of the ICSI program is COS after the appropriate preparation of the women. Accordingly, we give the source data of the state of the ovulatory phase for 180 virtually healthy women from couples with male infertility after one cycle of ovarian stimulation (Table 2).

The data in Table 2 are given taking into account the peculiarities of the male infertility (oligoasthenozoospermia, obstructive and non-obstructive azoospermia) in order to prove the similarity of the general background of reproductive function of women and guarantee the probability of interpretation of the results of the effectiveness of the applied ICSI program. At once we will note that there was no lack of response to stimulation in any case, there was no lack of oocytes in the transvaginal puncture. According to the analysis of the Table 2, it is fair to say that no statistically significant changes were found when comparing the basic parameters.

Then we will comment directly the main indicators of the early stage of embryogenesis, the features of which are quite naturally caused by the form of spermatogenesis disorder and the kind of pathospermia, which can be clearly seen in Table. 3.

As can be seen from the data in the Table 3, significantly less fertilized oocytes were obtained in patients with non-obstructive azoospermia. Accordingly, the percentage of oocytes with no fertilization among the latter is the largest: 48.0±4.1% versus 24.6±4.5% and 22.0±2.4% with obstructive azoospermia and oligoasthenozoospermia respectively (p<0.05). We focus on the process of fission as the main fact of the procedure. At virtually the same ratio of the percentage of oocytes with fertilization and without it, the initial number of zygotes per 24 hours is fairly less in non-obstructive azoospermia, namely 3.1±0.5 versus 4.4±0.4 and 5.0±0.3 in obstructive azoospermia and oligoasthenozoospermia. This situation directly affects the number of embryos at the stage of 48 hours (2,6±0,5 versus 3,9±0,4 and 4,5±0,2, respectively, p<0,05) and was initially manifested at the stage of 72 hours (1.7±0.1 versus 3.1±0.2 and 3.8±0.1, respectively, p <0.05). As a result, blastulation at the stage of 120 hours from one cycle was in the group with oligoasthenozoospermia 3,6±0,2, it was 1.3 times less in obstructive azoospermia and 2.3 times in comparison with the previous value in the non-obstructive form.

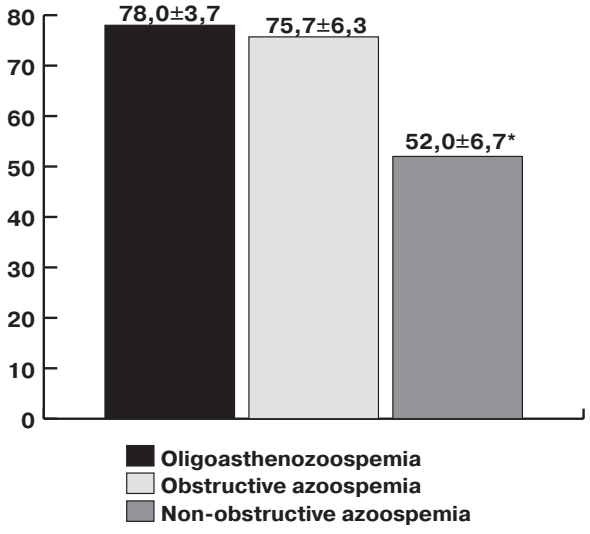

Fig. 1. Percentage of fertilized oocytes of women in cases of men with oligoasthenozoospermia, obstructive and non-obstructive azoospermia in the ICSI program

Summarizing the abovementioned data, we emphasize the main ones – the Figure 1 demonstrates the percentage of fertilized oocytes of women with different types of spermatogenesis disorders. It was fairly less in non-obstructive azoospermia (52.0±10.1% versus 75.7±6.9% and 78.0±3.7% respectively, in obstructive azoospermia and oligoasthenozoospermia). Absence of fertilization was observed in 24 of 428 cycles, which was 5.7%. It is also important that the largest number of such cases, along with the smallest percentage of zygote fission and the number of embryos, especially at the stage of 72 hours in the group with non-obstructive azoospermia had a negative effect on the end result – less blastulation at the stage of 120 hours (1,2±0,4) than in non-obstructive azoospermia (2,8±0,1) and oligoasthenozoospermia (3,6±0,2); p<0.05.

The data obtained at the early stage of the fertilization procedure under the ICSI program have been reflected in the Table 4.

Table 4

Key indicators of early embryo implantation under ICSI program in the native cycle in couples with male infertilitytaking into account the type of pathospermia

Parameters	Types of pathospermia		
	Oligoasthenozoospermia, n=120	Obstructive azoospermia, n=38	Non-obstructive azoospermia, n=22
Number of embryos per 120 hours	432	106,4	26,4
Number of transferred embryos to the day of cultivation	204	72,2	26,4
Average number of transferred embryos per 1 embryo transfer	1,7±0,2	1,9±0,8	1,2±0,1
Number of implantation processes (biochemical and clinical pregnancy rate)	54	16	7

Note: * – the difference is reliable between the indicators; $p<0.05$.

Table 5

Indicators of pregnancies in couples with male infertility, taking into account the type of pathospermia under the results of the first cycle of ICSI program

Parameters	Types of pathospermia					
	Oligoasthenozoospermia, n=120		Obstructive azoospermia, n=38		Non-obstructive azoospermia, n=22	
	Abs.	%	Abs.	%	Abs.	%
Pregnancy, in total/including:	51	42,5	15	39,4	6	27,3
twins	12	23,5	3	20,0	1	16,6
triplets	1	1,9	1	6,7	0	

As can be seen from Table. 4, more embryos were transferred to the patients in native cycle in groups with men with oligoasthenozoospermia and obstructive azoospermia. This was reflected in the frequency of implantations. The percentage of biochemical pregnancies per stimulated cycle: 31.8%; 42.1% and 45.0% for non-obstructive, obstructive azoospermia and oligoasthenozoospermia, respectively. The number of women with biochemical/clinical pregnancy rate was 7, 16 and 54, respectively. In total, this was 42.8±3.6% (77 of 180 couples). Indicators of the realized pregnancy in women from infertile couples with male factor, taking into account the nature of the spermatogenesis disorder, are presented in Fig. 2.

Below, we analyze pregnancy rates in couples with male infertility (Table 5).

The Table 5 demonstrates that the percentage of pregnancy rate in case of embryo transfer in the non-obstructive azoospermia is less virtually by 1.5 times more than the other ones. The smallest in this group was the percentage of multiple pregnancy, which is a consequence of small number of embryos to a certain extent and their ability to implantation due to the poor quality of their maturity. The reproductive losses are worth noting. They occurred in 5 cases.

The embryos of the cryocycle were applied later. The Table 6 presents the main indicators of early implantation of embryos in women from the couples with male infertility in the ICSI program using cryocycles.

The Table 6 and those given above suggest the following. Thus, among the married couples with infertility caused by oligoasthenozoospermia in men in two cycles, the pregnancy occurred in 68 of 120 cases (56.7±4.5%), in obstructive azoospermia the pregnancy occurred in 22 of 38 (57.9±8.0 %) cases and in non-obstructive azoospermia the pregnancy occurred in 7 of 22 (31.8±9.9%); the latter figure is fairly less than the previous two. As a result of total, it was found that in 97 of 180 couples the applied ICSI program resulted in pregnancy, which was 53.9±3.7%.

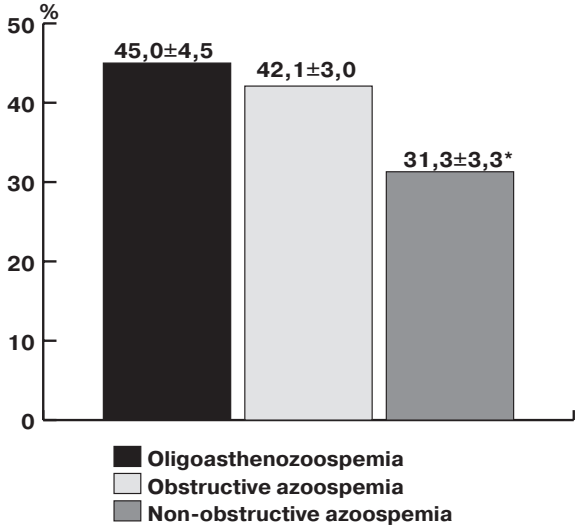

Fig. 2. Percentage of pregnancies in married couples with male infertility, depending on the type of pathospermia under ICSI program

At the same time, when assessing the effectiveness of the implemented ICSI program, the final results are important. Their criteria were the percentage of reproductive losses and live births (Table 7).

As can be seen from Table. 7, the largest losses were in the group with non-obstructive azoospermia, they were three times higher than those in the other two groups. In the total number of couples (180) – 92 (51,1±3,7%) the pregnancy ended with the birth of a child; in the group with oligoasthenozoospermia, the value was 54.2±4.5% (in 65 of 120), obstructive azoospermia – 55.3±7.5% (21 of 38), non-obstructive azoospermia – 27.3±9.0%

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Table 6

Main indicators of the embryo implantation in the ICSI program, when using cryocycles

Parameters	Types of pathospermia		
	Oligoasthenozoospermia, n=66	Obstructive azoospermia, n=22	Non-obstructive azoospermia, n=15
Number of couples with embryos	36	16	0
Total number of embryos	43,2	14,4	0
Average number of embryos per 1 embryo transfer	1,2±0,1	0,9±0,1	0
Number of implantation processes (biochemical and clinical pregnancy rate)	14	6	0
Pregnancy percentage	38,8±8,1	37,5±12,1	0

Table 7

The final results of the ICSI program (n = 180)

Parameters	Total, absolute number	Including		
		Oligoasthenozoospermia, n=66	Obstructive azoospermia, n=22	Non-obstructive azoospermia, n=15
Clinical pregnancy	97	68	22	7
Missed miscarriage	4	2	1	1
Lost pregnancy	1	1	-	-
Reproductive losses, absolute number, %	5 5,2	3 4,4	1 4,5	1 14,3
Live births	92	65	21	6

(6 of 22); the latter value is less reliable. Note that the remaining couples (88) were offered a repeated cycle, to which 37 (42.0%) couples agreed, and to other couples (51–58.0%) the ICSI program was recommended.

Thus, a comparative analysis of the results of the ICSI program in cases of male infertility has demonstrated that its effectiveness was close in among themselves in groups with oligoasthenozoospermia and obstructive azoospermia. The pregnancy with subsequent childbirth has been achieved in more than half of the cases. At the same time, the lack of desirable results in the second half of couples, as well as low values of the program applied in non-obstructive azoospermia (only every third person with positive data) leaves the issue of the provision of assisted reproductive technology relevant. Today, the solution to this issue is connected to a greater extent with the optimization of the selection of an adequate option of assisted reproductive technology, improved selection criteria. In addition, the possibility of predicting the final results becomes significant through the comprehensive assessment of health and, in particular, the reproductive health, taking into account the risk factors.

CONCLUSION

It was found that the overwhelming majority of men who are infertile in married couples and applied the ICSI program for the birth of a child were at the age of 30 and 30–39 years old (41.7±3.6% and 42.7±3.6%, respectively), whereas women at the age of 30–39 years old (54.4±3.6% and 40.0±3.4% up to 30 years old) were more, and the men at the age of 40 years and older were three times more (15.6±2,7%, women – 5.5±1.6%; $p<0.05$).

It has been established that any statistically significant changes in the basic parameters of the source data of the follicular and ovarian phases after the cycle of ovarian stimulation from infertile couples with the various types of male pathospermia have not been proved.

The specificity of the process of fertilization of oocytes and their fission is observed, depending on the spermatogenesis disorder – the fertilization rate is fairly lower in non-obstructive azoospermia (52.0±10.1% versus 75.7±6.9% and 78.0±3.7% in obstructive azoospermia and oligoasthenozoospermia), a significant difference was observed in the number of embryos at the fission stage of 72 hours (1.7±0.1% versus 3.1±0.1% and 3.8±0.1%, respectively; $p<0.05$), as a result of which the largest number of blastulations at the stage of 120 hours of one cycle was found in oligoasthenozoospermia (3,6±0,2%), 1.3 times less in obstructive azoospermia and 2.3 times less in non-obstructive azoospermia.

The total percentage of biochemical pregnancies per stimulated native cycle was 42.8±3.6% (77 of 180 couples) and was almost the same in the group of men with oligoasthenozoospermia and obstructive azoospermia (45.0±4.5% and 42.1±8,0%, respectively) and only in every third couple with non-obstructive form (31.8±9.9%); it was the same but less by 14% in the first two cases with cryocycles (38.8±8.1% and 37.5±12.1%, respectively). After reproductive losses, which were the highest in non-obstructive azoospermia (14.3% vs. 4.5% in other types), 92 (51,1±3.7%) children were born. The peculiarities in terms of the type of male pathospermia were found: in case of oligoasthenozoospermia, the value was 54.2±4.5% (in 65 of 120), obstructive azoospermia – 55.3±7.5% (in 21 of 38), in case of non-obstructive azoospermia they were significantly less – 27,3±9.0% (6 of 22).

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