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PERSONIFIED CORRECTION OF MICRONUTRIENT DEFICIENCY AS A THERAPEUTIC TACTIC FOR IMPROVING THE QUALITY OF EJACULATE IN IDIOPATHIC INFERTILITY

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Introduction. Marital infertility is one of the key medical problems. Almost 50% of infertility in marriage is caused by male infertility. The proportion of idiopathic male infertility is 30–40%. **Material and methods.** 157 patients with idiopathic infertility were randomized into 2 groups. The main group (MG) (n = 82): conducted a correction of the level of micronutrients in case of their deficiency by the appointment of monocomponent drugs in the maximum permitted daily doses. The control group (n = 75) (empirical therapy with complex drugs) was randomized to subgroup 1 (CG1) (n = 38): complex preparations with L-carnitine were used; and subgroup 2 (CG2) (n = 37): complex multivitamin preparations without L-carnitine were used. To identify micronutrient deficiencies, 93 healthy volunteers who realized a fertile function were examined (their partners were in the third trimester of pregnancy). **Results.** Deficiencies of micronutrients were determined: selenium, zinc, vitamins C and E. Correction was carried out for three months with monocomponent preparations. In the exhaust gas, there was a positive dynamics in all parameters of the spermogram. In the control subgroups the ejaculate volume, concentration, total sperm count did not change, an increase in the general and progressive motility was revealed. The proportion of normal spermatozoa increased in MG, CG1 and CG2 groups by 61.9%, 28.6% (in comparison with MG $p < 0.01$) and 20.0% (in comparison with MG $p < 0.001$), respectively. Total mobility increased – by 44.5%, 24.5% (compared to MG $p < 0.05$), by 12.0% (compared to exhaust gas $p < 0.001$), respectively. Progressive mobility – by 60.4%, 54.5% (compared with MG $p > 0.05$), 14.7% (compared with MG $p < 0.001$), respectively. Pregnancy in MG was 21.9%, in CG1 – 5.2% ($p < 0.05$) and CG2 – 2.7% ($p < 0.05$). **Conclusion.** Personified correction of micronutrient deficiency in order to improve the quality of ejaculate in idiopathic male infertility was an effective therapeutic tactic. The results obtained suggest that this approach is more pathogenetically justified, which requires further study.

Keywords: male infertility; micronutrient deficiency; fertility; vitamins; trace elements.

ПЕРСОНИФИЦИРОВАННАЯ КОРРЕКЦИЯ МИКРОНУТРИЕНТНОГО ДЕФИЦИТА КАК ЛЕЧЕБНАЯ ТАКТИКА УЛУЧШЕНИЯ КАЧЕСТВА ЭЯКУЛЯТА ПРИ ИДИОПАТИЧЕСКОМ БЕСПЛОДИИ

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Введение. Бесплодие в браке одна из ключевых медицинских проблем. Мужское бесплодие практически в 50 % случаев является причиной бесплодия в браке. Доля идиопатического мужского бесплодия составляет 30–40 %. **Материал и методы.** 157 пациентов с идиопатическим бесплодием рандомизированы на 2 группы. Основная группа (ОГ) (n = 82): проводили коррекцию уровня микронутриентов при их дефиците назначением монокомпонентных препаратов в максимальных разрешенных суточных дозах. Контрольная группа (n = 75) (эмпирическая терапия комплексными препаратами) была рандомизирована на подгруппу 1 (КП1) (n = 38): применяли комплексные препараты с L-карнитином; и подгруппу 2 (КП2) (n = 37): применяли комплексные поливитаминные препараты без L-карнитина.

Для выявления дефицитов микронутриентов обследовали 93 здоровых добровольца, реализовавших фертильную функцию (их партнерши находились на III триместре беременности). **Результаты.** Определены дефициты микронутриентов: селен, цинк, витамины С и Е. Проведена коррекция в течение трех месяцев монокомпонентными препаратами. В ОГ положительная динамика была по всем параметрам спермограммы. В контрольных подгруппах не изменились объем эякулята, концентрация, общее количество сперматозоидов, выявлен прирост общей и прогрессивной подвижности. Доля нормальных сперматозоидов увеличилась в ОГ, КП1 и КП2 на 61,9, 28,6 (в сравнение с ОГ $p < 0,01$) и 20,0 % (в сравнении с ОГ $p < 0,001$) соответственно. Общая подвижность увеличилась: на 44,5, 24,5 (в сравнении с ОГ $p < 0,05$), на 12,0 % (в сравнении с ОГ $p < 0,001$) соответственно. Прогрессивная подвижность: на 60,4, 54,5 (в сравнении с ОГ $p > 0,05$), 14,7 % (в сравнении с ОГ $p < 0,001$) соответственно. В ОГ беременность наступила в 21,9, в КП1 — в 5,2 ($p < 0,05$) и КП2 — в 2,7 % ($p < 0,05$). **Заключение.** Персонифицированная коррекция дефицита микронутриентов с целью улучшения качества эякулята при идиопатическом мужском бесплодии явилась эффективной лечебной тактикой.

Ключевые слова: мужское бесплодие; дефицит микронутриентов; фертильность; витамины; микроэлементы.

INTRODUCTION

Every year, approximately 15% of married couples seek medical help for an infertility problem in the marriage, and approximately half of infertility cases in marriage are associated with the male factor [1]. Recently, various expert groups have published recommendations for the diagnosis and treatment of male infertility, although there is no consensus regarding the patient management strategies [2]. Male infertility can occur due to several causes, including sexual disorders, urogenital tract infections, congenital anomalies, varicocele, endocrine causes, chronic diseases, and immunological factors [3–5].

Despite the large number of studies and achievements in reproductive andrology, a high incidence of idiopathic infertility still remains, accounting for 30%–40% of infertility cases [4, 6]. The effectiveness of an empirical therapy for idiopathic male infertility does not exceed 30% [7]; therefore, the search for possible causes of male infertility, which lead to a deterioration in the quality of the ejaculate, and ways to eliminate them remain relevant.

Nowadays, a significant portion of the data suggests the predominant role of oxidative stress in the etiology of idiopathic male infertility [8, 9]. On the background of an oxidative stress, activated lipid peroxidation of the plasma membrane of sperm cells increases sperm DNA fragmentation, which leads to a decrease in the fertilization rate and frequency of pregnancies, and a disruption of the embryonic development [10, 11].

With the increasing recognition of the role of oxidative stress in the pathophysiology of male infertility, the role of antioxidants as one of the treatment options for idiopathic male infertility has also increased [12]. The most proven approach in the treatment of idiopathic male infertility is the use of multicomponent dietary supplements. It is believed that the multicomponent drug is more effective in the treatment of pathospermia due to the synergistic effect of its ingredients [6]. Their main component is L-carnitine, an antioxidant that absorbs superoxide anions and peroxide radicals, thereby inhibiting lipid peroxidation [13]. Due to the ability to transport fatty acids to the mitochondria, L-carnitine affects energy metabolism and sperm motility [14].

According to a number of studies, oxidative stress occurs due to a change in the environment, lifestyle, and diet, which leads to a deficiency or violation in the exchange of vitamins and trace elements [15–17].

The increase in the prevalence of male infertility occurs against a background of significant changes in the nature of modern men's nutrition, including the excessive energy value of the diet with a significant deficit in the consumption of vitamins, trace elements, and dietary fibers [18, 19]. In this regard, we suggest that the correction of identified deficits by supplementing with the specific deficient substances will provide a pathogenetically based treatment and avoid empirical treatment with multicomponent drugs.

Research aim. To evaluate the effectiveness of a personalized correction of micronutrient deficiency in pathospermia.

MATERIALS AND METHODS

The study involved 157 men, aged above 18 years (on average 33.7 ± 5.4 years), who complained of the inability to conceive in marriage for more than 12 months, with the detection of pathospermia in two or more consecutive analyses of the ejaculate conducted at intervals of at least two weeks (focused on the best of them) [3]. All the patients permanently resided in the Omsk region and agreed to participate

in the study and to provide their personal data for analysis.

Criteria for non-inclusion in the study: azoospermia; cryptozoospermia; cryptorchidism; infectious mumps combined with orchitis in the anamnesis; endocrine pathology associated with male infertility; established genetic causes of infertility; pyospermia and/or clinically significant growth of the microflora in the ejaculate; sexually transmitted infections (analysis of urethral discharge by polymerase chain reaction for *Ureaplasma spp.*, *Mycoplasma hominis*, *Mycoplasma genitalium*, *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, *chlamydia trachomatis*, *cytomegalovirus*, *herpes simplex* type 1, 2); systemic diseases (diabetes mellitus, chronic kidney failure, systemic lupus erythematosus); taking glucocorticosteroids; patients with cancer; immune infertility confirmed by performing a MAR test; as well as taking multivitamins and/or antioxidant drugs in the past six months.

The levels of vitamins A, B9, D, E, and C in the blood of the study participants were determined using a high-performance liquid chromatography, and their hair was tested for selenium and zinc by atomic absorption spectrometry.

Patients were randomized into two groups. In the main group (n = 82), personalized correction of micronutrient levels was performed in accordance with the identified deficiencies of the patients (critically low levels) by prescribing specific monocomponent drugs in the maximum permitted daily doses (according to the official instructions for the drug). In the control group (n = 75), an empirical therapy was performed using complex drugs that are freely available in the pharmacy chain. The control group was further divided into subgroups: subgroup 1 (n = 38) – patients took complex medications containing L-carnitine and subgroup 2 (n = 37) – patients took complex multivitamin agents without L-carnitine in their composition.

The treatment course in all the groups was 3 months [7]. The comparative characteristics of the groups are presented in table 1.

There were no statistical differences between subgroups 1 and 2, as well as between the control and the main group. In addition, to identify specific micronutrients deficiencies (critically low levels), 93 healthy volunteers who had proven their fertility function (at the time of participation in the study, their partners were at least in the third trimester of pregnancy) were additionally examined. At the same time, the quality of the ejaculate was deliberately not evaluated, putting the realization of the couple's fertile potential at the forefront.

The effectiveness of the treatment was evaluated by two criteria: improvement in the qualitative and

Table 1 / Таблица 1

Characterization of patients of the main and control groups (n = 157)
Характеристика пациентов основной и контрольной групп (n = 157)

The parameter under study	Main group (n = 82)	Control group (n = 75)	Level p
Age, years	33.6 ± 5.2 (33; 32.4–34.8)	33.8 ± 5.7 (33; 32.5–35.1)	>0.05
Experience of infertility, years	3.4 ± 2.2 (3; 2.9–3.9)	3.5 ± 2.3 (3; 2.9–4)	>0.05
Volume of ejaculate, ml	3.3 ± 1.4 (3.1; 2.9–3.6)	3.1 ± 1.3 (3; 2.7–3.4)	>0.05
Sperm concentration, mln/ml	54.6 ± 46.2 (45; 44.5–64.8)	62.5 ± 49.5 (46.1; 51.1–73.9)	>0.05
Total number of sperms, mln	152.0 ± 117.9 (135; 126.1–177.9)	182.4 ± 131.3 (147.5; 152.1–212.6)	>0.05
Overall mobility, %	34.8 ± 12.6 (32; 32.0–37.5)	35.5 ± 10.1 (39.6; 33.2–37.9)	>0.05
Progressive mobility, %	21.2 ± 8.8 (19.8; 19.2–23.1)	21.1 ± 12.0 (23; 18.4–23.9)	>0.05
Morphology, % by Kruger	2.1 ± 0.7 (2; 1.9–2.3)	2.3 ± 0.9 (3; 2.1–2.5)	>0.05

Note. All values are represented as the average value (M) ± standard deviation (m) (median; 95% confidence interval).

quantitative indicators of the ejaculate (3 months after the start of the therapy) and pregnancy of the spouse (observation of the couple for 6 months from the start of the therapy).

Statistical analysis of the results using nonparametric methods was done using the Statistica 10.0 software package. In the statistical analysis, the critical level of significance of p was assumed to be 0.05. The data is presented as $M \pm m$, where M is the average and m is the standard deviation.

RESULTS

Critical micronutrient deficiencies were identified in the first stage of the study (tables 2, 3).

Statistically significant differences were found for selenium, zinc, and vitamins C and E. This fact needs to be confirmed in a further study, since it was beyond the scope of the current study. A separate comment is required for the detected increase in the level of selenium in the hair, which indicates an increase in the level of its metabolism and excretion in order to compensate for the increased intake of xenobiotics, including heavy metal salts, and indicates its predeficit or deficit state [20].

Thus, patients were prescribed one or more of the following substances: vitamin E at a dose of 100 mg, once a day; vitamin C at a dose of 250 mg, 2 times a day; zinc picolinate at a dose of 22 mg, once a day; selenium at a dose of 100 mcg, once a day.

At the end of the three-month course, the dynamics of the spermogram indicators in the patients of the main and control groups was analyzed (table 4–6).

In the patients of the main group, a positive trend was recorded for all the estimated parameters with a high degree of confidence ($p < 0.001$), while only the sperm count and volume of ejaculate, had a slightly lower reliability ($p < 0.05$), which does not reduce the value of the results. More interesting is the comparison of these changes with the control subgroups.

Thus, in both control subgroups, there were no changes in the volume of ejaculate, concentration and total number of spermatozoa, but there was a statistically significant increase in the total and progressive mobility, as well as an increase in the number of morphologically normal spermatozoa.

Despite the differences at the baseline level, it is interesting to compare the severity of these changes in the study groups, since the changes are quite clear. Thus, the proportion of normal sperms according to Kruger increased in the patients of the main group and the 1st and 2nd control subgroups, respectively, by 61.9, 28.6 (compared with the main group $p < 0.01$), and 20.0% (compared with the main group $p < 0.001$).

Unidirectional changes were also recorded in terms of mobility. For patients of the main group and the 1st and 2nd control subgroups, total mobility increased by 44.5, 24.5 (compared to the main group $p < 0.05$),

Table 2 / Таблица 2

Comparison of micronutrient levels in patients included in the study and healthy volunteers, $M \pm m$

Сравнение уровня содержания микронутриентов в крови у пациентов, включенных в исследование, и здоровых добровольцев, $M \pm m$

The parameter under study	Research participants (n = 157)	Healthy volunteers (n = 93)	Level p
Vitamin A, mcg ml	0.45 ± 0.11	0.43 ± 0.08	>0.05
Vitamin B_9, ng/ml	7.79 ± 2.08	7.90 ± 2.69	>0.05
Vitamin C, mcg/ml	3.56 ± 0.94	9.19 ± 3.64	<0.001
Vitamin D, ng/ml	24.0 ± 7.78	25.3 ± 9.78	>0.05
Vitamin E, mcg/ml	5.39 ± 1.29	8.96 ± 2.23	<0.001

Table 3 / Таблица 3

Comparison of the level of metals in patients included in the study and healthy volunteers, $M \pm m$

Сравнение уровня содержания металлов в волосах у пациентов, включенных в исследование, и здоровых добровольцев, $M \pm m$

The parameter under study	Research participants (n = 157)	Healthy volunteers (n = 93)	Level p
Selenium, mcg/g	1.11 ± 0.20	0.99 ± 0.29	<0.001
Zinc, mcg/g	160.91 ± 36.93	184.42 ± 43.56	<0.001

Table 4 / Таблица 4

Dynamics of spermogram indicators of patients of the main group (*n* = 82)

Динамика показателей спермограммы пациентов основной группы (*n* = 82)

Indicator	Before treatment	After treatment	Level *p*
Volume of ejaculate, ml	3.3 ± 1.4 (3.1; 2.9–3.6)	3.6 ± 1.0 (3.7; 3.4–3.9)	<0.05
Sperm concentration, mln/ml	54.6 ± 46.2 (45; 44.5–64.8)	60.0 ± 28.2 (56.8; 53.8–66.2)	<0.05
Total number of spermatozoa, mln	152.0 ± 117.9 (135; 126.1–177.9)	216.0 ± 104.7 (200; 193.8–239.8)	<0.001
Overall mobility, %	34.8 ± 12.6 (32; 32.0–37.5)	50.3 ± 10.0 (49.5; 48.1–52.5)	<0.001
Progressive mobility, %	21.2 ± 8.8 (19.8; 19.2–23.1)	34.9 ± 12.9 37; 32.0–37.7)	<0.001
Morphology, % by Kruger	2.1 ± 0.7 (2; 1.9–2.3)	3.4 ± 1.0 (3; 3.2–3.7)	<0.001

Note. All values are represented as *M* ± *m* (median; 95% confidence interval).

Table 5 / Таблица 5

Dynamics of spermogram indicators of patients in the control subgroup 1 (*n* = 38)

Динамика показателей спермограммы пациентов контрольной подгруппы 1 (*n* = 38)

Indicator	Before treatment	After treatment	Level *p*
Volume of ejaculate, ml	2.9 ± 1.1 (2.9; 2.5–3.3)	3.2 ± 1.1 (2.8; 2.8–3.6)	>0.05
Sperm concentration, mln/ml	66.2 ± 47.8 (54.8; 50.5–81.9)	73.6 ± 52.8 (51.6; 56.2–90.9)	>0.05
Total number of spermatozoa, mln	190.6 ± 123.6 (168.4; 150.0–231.3)	253.1 ± 235.9 (187.7; 175.5–330.6)	>0.05
Overall mobility, %	33.5 ± 10.3 (36.3; 30.0–36.9)	41.7 ± 15.4 (39.8; 36.7–46.8)	<0.05
Progressive mobility, %	19.1 ± 11.8 (22.0; 15.2–23.1)	29.5 ± 13.0 (31.5; 25.2–33.8)	<0.05
Morphology, % by Kruger	2.1 ± 0.9 (2; 1.8–2.4)	2.7 ± 0.9 (3; 2.4–3.0)	<0.05

Note. All values are represented as *M* ± *m* (median; 95% confidence interval).

Table 6 / Таблица 6

Dynamics of spermogram indicators of patients in the control subgroup 2 (*n* = 37)

Динамика показателей спермограммы пациентов контрольной подгруппы 2 (*n* = 37)

Indicator	Before treatment	After treatment	Level *p*
Volume of ejaculate, ml	3.2 ± 1.5 (3.0; 2.7–3.7)	3.5 ± 1.6 (3.0; 2.9–4)	>0.05
Sperm concentration, mln/ml	58.7 ± 51.6 (46.1; 41.4–75.9)	67.6 ± 52.5 (40.8; 50.0–85.1)	>0.05
Total number of spermatozoa, mln	173.9 ± 139.9 (131.9; 127.2–220.6)	216.1 ± 177.3 (187.7; 157.0–275.3)	>0.05
Overall mobility, %	37.6 ± 9.6 (41.7; 34.4–40.8)	45.2 ± 14.0 (43.8; 40.5–49.9)	<0.05
Progressive mobility, %	23.2 ± 12.0 (23.1; 19.2–27.2)	34.2 ± 12.3 (32.9; 30.0–38.3)	<0.01
Morphology, % by Kruger	2.5 ± 0.9 (3; 2.2–4)	3.2 ± 0.8 (3; 3.0–3.6)	<0.05

Note. All values are represented as *M* ± *m* (median; 95% confidence interval).

and 12.0% (compared to the main group $p < 0.001$), respectively; the progressive mobility also increased by 60.4, 54.5 (compared to the main group $p > 0.05$), and 14.7% (compared to the main group $p < 0.001$), respectively.

It is important to note that in the main group, pregnancy occurred for 18 (21.9%) out of 82 couples, which was significantly more frequent than in the control subgroup 1 (2 cases (5.2%) out of 38 [$\chi^2 = 3.94$, $p < 0.05$)] and subgroup 2 [1 case (2.7%) out of 37 ($\chi^2 = 5.48$, $p < 0.05$)].

DISCUSSION

There is no doubt that oxidative stress plays an important role in the pathophysiology of idiopathic male infertility [11]. The balance of reactive oxygen species and antioxidant systems establishes a redox homeostasis, which is necessary for the normal functioning of a spermatozoa. Excessive production of reactive oxygen species reduces the concentration of antioxidants and leads to the development of oxidative stress in the sperm, considered as one of the main factors of male infertility [6]. Basic recommendations for the correction of oxidative stress are primarily aimed at eliminating the provoking conditions, including smoking, obesity, alcohol consumption, hypodynamia, varicocele, infection of the reproductive system, and gonadotoxic hyperthermia [21]. The most frequently used and discussed treatment option for the male factor in an infertile couple, including idiopathic infertility, is the use of antioxidant drugs [10, 12]. This group of drugs has a certain level of effectiveness and does not have serious side effects [11]. At the same time, the level of reactive oxygen species in the sperm should not be completely suppressed, as this can worsen the capacitation and hyperactivity of a spermatozoa [21].

While there is an extensive literature on the positive effects of oral antioxidants on ejaculate parameters [6–9, 11–14, 16], some authors report that there is no proven positive effect of an antioxidant therapy for male infertility [21, 22]. Most published studies do not provide clear conclusions regarding the optimal drug [7, 23, 24]. Currently, no study has established the best drug, dose, and duration of therapy. In most studies, the effect of the drug on spermogram parameters is estimated, but the assessment of a pregnancy in the couple is often not carried out [6]. Thus, there is still no consensus on the clinical effectiveness of an antioxidant therapy in the treatment of male infertility, and therefore, it remains relevant to further search for the possible causes of pathospermia and the ways to correct them.

This study was conducted to evaluate the effectiveness of a personalized correction of a micronutrient deficiency as a therapeutic strategy to improve the quality of the ejaculate in idiopathic infertility. Micronutrient deficiency is of interest in the aspect of the necessity and justification of taking certain multicomponent antioxidant drugs when conducting an empirical therapy for patients with male infertility. Such preparations contain a number of ingredients related to the antioxidant system as a whole [7, 14]. However, due to technological and legislative features, the content of each individual ingredient is not high and is focused on the consumption standards of a healthy person. In our case, we are dealing with sick persons who lack very specific micronutrients (vitamins, metals), and their deficiencies can be measured. This was done in our study, taking into account the geographical factor. All the study participants were permanently residing in the territory of the Omsk region. A fairly narrow range of micronutrients was identified, the lack of which was critically significant: selenium, zinc, and vitamins C and E. As a result of the three-month course of one or more monocomponent drugs (solved individually) for patients of the main group, a statistically significant (from $p < 0.05$ to $p < 0.001$) improvement in all the parameters of the ejaculate was obtained. It is particularly valuable that spontaneous pregnancy was more frequent in the main group (21.9%) during the six months monitoring than in the control subgroup 1 (2.7%–5.2%, $p < 0.05$) and subgroup 2 (1 case (2.7%) out of 37 ($\chi^2 = 5.48$, $p < 0.05$).

However, in the control subgroups, positive changes were found, but only in terms of the motility and morphology of the sperms, without changes in the volume and concentration. Control subgroups were formed in an effort to account for the possibility of taking both L-carnitine-containing and non-L-carnitine-containing complexes. The degree of improvement, although statistically significant, was less expressed in comparison with the main group. In the main group, the improvement in quality indicators was noted on average by two or more times compared to the initial values, after taking L-carnitine-containing complexes-$^1/_3$–$^1/_4$; after taking multivitamin complexes – by $^1/_5$–$^1/_{10}$.

Only by changing the progressive mobility of a sperm, the indicators of the patients in the main group and control subgroup 1 had similar results: an improvement of 60.4 and 54.5% ($p > 0.05$), respectively. It is known that L-carnitine plays a key role in providing a sperm with the energy necessary for maturation and mobility [6, 7]. This can explain the observed increase in progressive mobility. Thus, point-to-point replenishment of the micronutrient level(s) in accordance with the identified critical deficit helps to restore the physiological process of sperm formation, thereby exerting a pathogenetically justified effect.

CONCLUSION

A personalized correction of micronutrient deficiency in order to improve the quality of ejaculate in idiopathic male infertility was an effective therapeutic strategy. The results suggest that this approach is more pathogenetically sound, which requires a further study.

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