Effectiveness of low level laser therapy for treating male infertility

Sergey Vladimirovich Moskvin1*, Oleg Ivanovich Apolikhin2

1 O.K. Skobelkin State Scientific Center of Laser Medicine under the Federal Medical Biological Agency, Moscow, 121165, Russia
2 N.A. Lopatkin Research Institute of Urology and Interventional Radiology, Moscow, 105425, Russia

Received 4th of February, 2018    Accepted 1st of March, 2018
© Author(s) 2018. This article is published with open access by China Medical University

ABSTRACT

In half of the cases, the infertility of the couple is due to the disorder of the male fertility. The leading factors that cause male infertility are urogenital infections, disorders of the immune system, testicular and prostate pathologies, as well as endocrine disorders. Low level laser therapy (LLLT) is an effective physical therapy method, used in many areas of medicine, including obstetrics and gynaecology, andrology and urology; and it is recommended as an integral part of the complex treatment of infertility.

The literature review showed that LLLT is beneficial in treating male infertility. Laser can significantly improve the survival, motility and speed of movement of spermatozoa. Laser therapy of patients with prostatitis and vesiculitis can eliminate infiltrative-exudative changes, improve reproductive and copulatory functions. Local illumination of red (635 nm) and infrared (904 nm) spectra should be combined with intravenous laser blood illumination (ILBI) of red (635 nm) and ultraviolet (UV) (365 nm) spectra.

Keywords:
Male infertility; Sperm motility; Low level laser therapy

1. Introduction

Translational medicine promotes a faster implementation of scientific achievements in the field of practical public health, allowing a personalization of treatment, which positively affects its results. This interaction was described as "Bench-to-Bedside" or "Bedside-to-Bench" [1]. This is an interdisciplinary field of modern medicine, based on the achievements of science: physiology, molecular biology, genetics and clinical research, created to ensure a higher efficiency of medical services.

Laser therapy is a vivid example of interdisciplinary medicine, which was based on the fundamental research in the field of physiology, biophysics and biochemistry, resulting in the emergence of highly effective therapeutic techniques that take into account the individual characteristics of the patient. However, it is only possible to see the full potential of laser therapy by strictly following the rules, approved by LLLT standards [2, 3] and using appropriate equipment.

Male infertility is a multifactorial syndrome that includes a wide range of disorders, a symptom of many different pathological conditions affecting both the sexual and other body systems: endocrine, nervous, blood, and immune [4-6].

According to the recommendations of World Health Organisation (WHO) (2000) [7], 16 main nosologies are distinguished, each of which, in turn, includes upwards of several dozen specific pathogenetic factors, 4 of 16 diagnoses are descriptive, without indicating the true cause: idiopathic oligo-, astheno-, terato- and azoospermia.

Sexually active couples, not protected during the year and not having had any children, according to WHO, are regarded as infertile. During the first year, about 25% of couples do not get pregnant. Of these, 15% seek medical help, and less than 5% do not succeed. In half of the cases, the infertility of the couple is due to the disorder of the male fertility. Causes of male infertility can be congenital or due to acquired abnormalities of the genitals, infections of the genitourinary system, increased scrotal temperature (varicocele), endocrine disorders, genetic abnormalities and immunological factors [8].

It is suggested that most idiopathic forms are genetically due to mutations and polymorphisms of many genes [4]. However, this hypothesis does not have rigorous proof and requires detailed studies [9]. Certainly, some pathologies are associated with a mutation, that is, damage to the DNA, but there is no doubt that in the overwhelming majority of cases, this is only the result of epigenetic changes in the genome that are reversible [10]. At the same time, it is known that low-intensity laser light not only effectively protects cells from DNA damage by various physical and chemical pathogenic factors, but is also able to activate "nec-
in many areas of medicine, including in obstetrics and gynaecology, but also has pronounced protective properties [11], and most recently years, not only has almost no contraindications and side effects, but also low level laser therapy, which has been actively developing in recent years, not only has almost no contraindications and side effects, but also has pronounced protective properties [11], and most importantly, demonstrates the highest effectiveness of treatment in many areas of medicine, including in obstetrics and gynaecology [30], andrology and urology [31-33] and is recommended as an integral part of the complex solution of the infertility problem [20], i.e., it is successfully applied by those specialists who somehow face the problem of infertility.

In many cases, childless partnerships are a problem for couples [20], but it is quite obvious that in order to study the issues of interaction between the parties, it is necessary to understand as closely as possible the corresponding violations inherent in each sex, and also to justify the possibility of using low level laser therapy. Therefore, in this article, only male infertility is considered, but with the prospect of also studying the possible influence of low-intensity laser illumination (LILI) on female fertility, including within the framework of solving some issues arising during in vitro fertilization (IVF).

Understanding the biomodulating processes that result from the absorption of LILI and the underlying methodology of low level laser therapy (LLLT), have allowed us to substantiate many methods, and also to optimize the already known ones in different fields of medicine. The primary mechanism of the LILI biomodulatory action is the response of the organism to non-specific, that is, not associated with specific acceptors, absorption of laser light in various cells, resulting in a short-term increase in the concentration of calcium ions in the cytosol, the propagation of waves of increased Ca$^{2+}$ concentration both in cells and in various tissues. Following this, an organism response develops (secondary mechanisms), which begins with the activation of Ca$^{2+}$-dependent processes [2, 34].

### 3. Experimental research

The action of the laser beam for the study of the various physiological processes that determine, in particular, the motility of spermatozoa began almost from the moment of the appearance of lasers [35]. Numerous studies confirm the positive influence of LILI on the spermatozoa of various animals, their motility and the content of adenosine triphosphate (ATP) increases [36–59], cell life expectancy increases [60] as well as the probability of fertilization increases [61, 62]. But it must be noted that the research conditions were significantly different, and the parameters of the laser illumination technique are not accurately described (Table 1), which does not allow assessing the reliability and reproducibility of these results.

It is the increase in Ca$^{2+}$ concentration, including that caused by laser illumination, that stimulates the work of the mitochondria and the synthesis of ATP [2, 63], which plays a key role in providing motility of spermatozoa [64-66]. The relationship between the Ca$^{2+}$-dependent release of NO (nitrogen oxide) in illuminated spermatozoa (optimal exposure 5 minutes) is also indicated with an increase in their activity [67], although it is more likely that this is only a secondary effect.

Most of the experiments were performed in vitro, but there are exceptions. In particular, M.D. Porras et al. (1986) [68] showed an increase in the number of spermatogonia and activation of spermatogenesis after the irradiation of mice testes with continuous infrared LILI. A significant increase in the production of testosterone by the interstitial cells of the testes of mice (Leydig cells) is also reported as a result of laser illumination by a red continuous LILI with a 633 nm wavelength [69-71].

Taha M.F. and Valorejerdi M.R. [72] performed laser illumination with continuous LILI with a 830 nm wavelength in modulated mode (power 30mW, frequency 300Hz) directly on...
Table 1 – Experimental studies on the effect of LILI on spermatogenesis and sperm quality.

| No | Experimental model | Results | Illumination parameters* | Reference |
|----|--------------------|---------|--------------------------|-----------|
| 1. | Stallions          | Activation of the sexual reflexes of stallions (reduction of the time of preparation for the mount by 2-3 times and the number of mounts expended for 1 ejaculate), an increase in the activity of spermatozoa and rate of fertilization of mares. | 1. 890  
2. pulsed  
3. 5-7 W  
4. –  
5. 500  
6. 0, 5-1 (–)  
7. -  
8. 10  
9. Daily  
10. Laser acupuncture and externally on the testes | Adamkovskaya M.V., 2004 [36] |
| 2. | Sperm, buffalo     | Increase of the semen quality parameters. Maximum improvement was observed after 4 minutes of exposure | 1. 532  
2. continuous  
3. 1 mW  
4. 1,32 mW/cm²  
5. -  
6. 1-5  
7. 0.076, 0.15 ,0.23, 0.31, 0.38 J/cm²  
8. -  
9. -  
10. from above, homogeneously | Abdel-Salam Z. et al., 2011 [39] |
| 3. | Sperm, dogs        | Improvement and maintenance of sperm motility over time, decrease of the L-lactate production rate. | 1. 655  
2. -  
3. 21.7 mW  
4. -  
5. -  
6. 103/154/258 s  
7. 4/6/10 J/cm²  
8. -  
9. -  
10. from above, homogeneously | Corral-Baqués M.I. et al., 2005 [40] |
| 4. | Sperm, dogs        | The most changes were observed when output power 49.7 mW was used: increase of the progressive velocity (VSL), average path velocity (VAP), linear coefficient (LIN), straightness (STR), wobble (WOB) and beat cross frequency (BCF) and reduction of the mean amplitude of lateral head displacement (ALH). The output power 6,84 mW was the only one to keep the same motility parameters 45 min after illumination. | 1. 655  
2. continuous  
3. 6,8/15,4/33,1/49,7 mW  
4. -  
5. -  
6. -  
7. 3,34 J (5.97 J/cm²)  
8. -  
9. -  
10. - | Corral-Baqués M.I. et al., 2009 [41] |
| 5. | Sperm, bulls       | No differences in motility parameters. Increase in ROS generation (with 5 mW compared to 7.5 and 10 mW, and with 10 min compared to 5 and 1 min of illumination). Illumination with 5 mW caused more acrosomal/plasma membrane damage, and an increase in the number of cell with intermediate and higher mitochondrial potential. | 1. 633  
2. -  
3. 5 / 7.5 / 10 mW  
4. -  
5. -  
6. 1, 5, 10  
7. 30, 150, 300 / 45, 230, 450 / 60, 300, 600 ml/cm²  
8. -  
9. -  
10. through a spatial filter, homogeneously | Dreyer T.R. et al., 2011 [43] |
| 6. | Sperm, sea urchin  | Effect on the locomotor activity of sperm, 2-5 times increasing the percentage of active cells depending on the time after exposure. | 1. LED 650 / laser 635  
2. -  
3. -  
4. 90, 250, 750 / 290 mW/cm²  
5. -  
6. -  
7. 0.07, 0.7, 7, 70 / 3 ml/cm²  
8. -  
9. -  
10. 19 LEDs matrix at a distance of 10 cm / at a distance of 12,5 cm | Drozdov A.L. et al., 2014 [44] |
7. Sperm, Echiuroid, *Urechis unicinctus*  
Enhancement of the respiratory rate of sperm in the presence of CO in proportion to the fluence rate. A sharp and large peak was observed at 430 nm, broad and small peaks at 530 and 570 nm.  

| Fluence Rate (fotons/cm²/s) | 1.350 nm |
|-----------------------------|----------|
| 400 (6.5 × 10¹⁵)           |         |
| 430 (9.9 × 10¹⁵)           |         |
| 450 (1.1 × 10¹⁶)           |         |
| 500 (1.0 × 10¹⁶)           |         |
| 530 (1.1 × 10¹⁶)           |         |
| 570 (1.0 × 10¹⁶)           |         |
| 600 (9.7 × 10¹⁵)           |         |
| 650 (7.9 × 10¹⁵)           |         |

Fujiwara A. *et al.*, 1991 [45]

8. Sperm, rabbit  
Illuminated samples during *in vitro* liquid storage better maintained motility, acrosome integrity and viability. Stimulation of the sperm mitochondrial respiratory chain increases the viability of sperm cells.

Iaffaldano N. *et al.*, 2010 [46]

9. Sperm, frozen/thawed, chicken, pheasant and turkey  
The possibility for restoration of motility of cryopreserved spermatozoa. Increase in sperm motility of turkey sperm, increase in COX activity in pheasant and turkey sperm

Iaffaldano N. *et al.*, 2013 [47]

10. Sperm, bulls  
Acceleration of Ca²⁺ transport. Laser can stimulate Ca²⁺ exchange through the cell membrane that causes transient changes in the cytoplasmic Ca²⁺ concentration which control motility and acrosome reaction in spermatozoa and can trigger mitosis in other cells.

Lubart R. *et al.*, 1992 [48]

11. Sperm, bovine  
An accelerated Ca²⁺ uptake by the mitochondria after He-Ne and inhibition after high intensity illumination. The ATP-dependent Ca²⁺ uptake by the sperm plasma membrane vesicles was not changed by 633nm and was enhanced by 780 nm.

Lubart R. *et al.*, 1996 [49]

12. Sperm, bulls  
Inhibition of Ca²⁺ uptake by sperm mitochondria and enhancement of Ca²⁺ binding to sperm plasma membranes.

Lubart R. *et al.*, 1997 [50]

13. Human sperm, patients with Asthenozoospermia  
Increase of progressive motility with 4 and 6 J/cm² at the times of 60 and 45 min, respectively.

Salman Yazdi R. *et al.*, 2014 [54]
### 14. Human sperm, normal subjects and patients with infertility disorders.

Stimulation of sperm motility (most effective with 32 J/cm²) but not velocity. Non-motile live spermatozoa probably are stimulated.

| 1. 647 | Sato H. et al., 1984 [56] |
| 2. - |
| 3. - |
| 4. - |
| 5. - |
| 6. 80/80/80/80/80/160 s |
| 7. 0.5 / 1.0 / 2.0 / 4.0 / 8.0 / 32 J/cm² |
| 8. - |
| 9. - |
| 10. - |

#### 15. Sperm, bulls

Modulation of bovine sperm function by 10 min illumination, increase of motility parameters and mitochondrial potential.

| 1. 633 | Siqueira A.F.P. et al., 2016 [57] |
| 2. continuous |
| 3. 5/7.5/10 mW |
| 4. 0.51 / 0.765 / 1.020 mW/cm² |
| 5. - |
| 6. 5, 10 |
| 7. 0.156, 0.312, 0.234, 0.468, 0.312, 0.624, J/cm² |
| 8. - |
| 9. - |
| 10. homogenously over the entire dish |

#### 16. Sperm, ram and fish (tilapia)

UV or blue light generates high levels of ROS, resulting in a decrease in motility and fertility. In tilapia sperm, red and white light, which induce low levels of ROS, were found to improve motility and fertilization, while in ram sperm, only red light slightly improved the motility to a small extent.

| 1. 400-800 / 660 / 360 / 294 |
| 2. - |
| 3. 40 / 10 / 1,5 / 0,1 mW/cm² |
| 4. - |
| 5. - |
| 6. - |
| 7. - |
| 8. - |
| 9. - |
| 10. - |

#### 17. Sperm, boars

Structural changes in boar semen elements, mainly in the lipid component.

| 1. 633 |
| 2. - |
| 3. 0.7-08, mW |
| 4. - |
| 5. - |
| 6. 15, 30, 60, 120 c |
| 7. - |
| 8. - |
| 9. - |
| 10. - |

#### 18. Spermatozoa, eggs, fertilized eggs, embryos, and larvae of Sea Urchin Paracentrotus lividus

LILI does not induce morphological damage on the irradiated P. lividus gametes whose zygotes generate normal embryos and larvae. Overstimulation of some sperm leading to an accelerated cleavage of sea urchin zygotes is not deleterious to a correct embryogenesis.

| 1. 808 |
| 2. continuous |
| 3. 1 / 3 W |
| 4. - |
| 5. - |
| 6. - |
| 7. 64 / 192 J/cm² |
| 8. - |
| 9. - |
| 10. in contact and perpendicular to the surfaces of an Eppendorf tube or a chamber of a multiwall plate |

* - sequence of the presentation of laser illumination parameters
1. wavelength, nm
2. mode of laser operation of the
3. power
4. power density
5. frequency, Hz
6. exposure per 1 zone (total time of procedure), min
7. energy density, J/cm²
8. number of procedures per course
9. periodicity
10. technique
the testes of Wistar rats. Both stimulating and spermatogenesis-inhibiting effects were demonstrated, depending on the power density and exposure of laser light. Errors of predecessors were repeated by other authors many years later, already working with completely unacceptable parameters on the testicles of rams and getting the expected negative result [2, 73]. Two important conclusions can be drawn from these studies: you do not need to concentrate the laser beam at a point, and it is also impermissible to shine for more than 1.5 minutes per zone. It is also not difficult to understand that exposure to high-intensity UV light is detrimental to cells [74]. Therefore, the selection of parameters for laser illumination in order to activate life processes must be approached with caution and preliminary justification.

Numerous studies indicate a direct relationship between an increase in intracellular Ca²⁺ concentration and the stimulation of the fertilizing capacity of spermatozoa in both animals and humans [48-51, 75-83]. It should be noted that in a number of works, conclusions are drawn (erroneous, in our opinion) about the leading role of reactive oxygen species (ROS) in the mechanisms of the biomodulating action of LILI [78, 79, 83-86]. But this is completely wrong, ROS are only secondary products of laser-activated cellular metabolism [2; 63], that is, a consequence, not a cause.

An increase in the concentration of Ca²⁺ causes the formation of ROS and the activation of antioxidant system as a whole, and not vice versa [87]. This is indirectly confirmed by the fact that the kinetics of the release of ROS depends on the energy, rather than on the power of LILI, and the most important component is the exposure [88], which can not be in the case of a direct photochemical reaction, when the power of a light source is more important. Moreover, direct experiments showed that ROS are released under the action of LILI by activation of Ca²⁺-dependent mechanisms [89, 90].

Laser biomodulation appears to be more efficient and less expensive technology, which can be used with a fairly good scientific basis to improve artificial insemination and the effectiveness of embryonic systems [38]. As a result of laser illumination in vitro, the quality of the semen of bulls, rabbits and poultry used increases after a prolonged storage in the frozen state: spermatozoa penetrating ability (capacitation) is increased, their acrosomal reaction is induced with decreasing percentage of dead cells [46, 47, 91-95].

It is necessary to pay attention to studies in which it has been shown that laser illumination with continuous LILI of the red spectrum (633 nm, 10 mW, light spot area 0.125 cm², exposure 1-5 s) of immature oocytes of cows in vitro negatively affects the process of their maturation [96], although this was not observed in other analogous observations [97-102]. Perhaps the whole point is in the parameters of the illumination techniques and the differences in the experimental models. This question needs to be studied additionally, but it is necessary to understand that exposure to laser light with high energy density can harm or even kill the embryo. This is a fact that has been known for a long time [103]. Therefore, to ensure the safe operation of lasers, it is necessary to be guided by the relevant regulatory documents, the data of numerous studies and common sense.

Another important well-known fact is that the emergence and passage of dozens (up to 50) of waves of an increased concentration of calcium ions released from the endoplasmic reticulum depot is the essential condition for fertilization throughout the entire ovum volume [104]. The mechanisms of realization and the physiological necessity of this are still unknown, although the phenomenon has been actively studied for many years [105, 106], but one thing is clear that LILI realizes its biomodulating properties through activation of Ca²⁺-dependent intracellular reactions, activating the same calcium depot. Consequently, laser illumination can potentially interfere with fertilization breaking the calcium transitions from the bound to the free state and vice versa. Perhaps, such specific processes peculiar only to oocytes somehow participate in the process of their maturation. While this is not known, we will therefore adhere to the point of view that we should avoid using any laser treatment technology on oocytes and egg cells.

Data from research conducted for animal breeding can be also used in medicine. Moreover, there is quite convincing evidence that low-intensity, both laser and incoherent light, can significantly improve the survival, motility and speed of movement of human spermatozoa [77, 79, 107-122].

4. Optimal selection of wavelength and laser mode

In most studies conducted on animals, illumination was carried out almost exclusively by continuous LILI in the red spectrum (633-650 nm), and much less frequently in other spectral ranges (Table 2).

| Wavelength, nm | Sources |
|----------------|---------|
| 532            | [39]    |
| 633-637        | [43]; [47]; [57]; [78]; [91]; [94]; [96]; [107]; [123] |
| 647            | [56]    |
| 655-660        | [40]; [41]; [92] |
| 780            | [50]    |
| 890-904        | [111]; [112]; [114] |

Only one study used a pulsed infrared laser (905 nm wavelength) with a power of 50W (pulse duration of 200 ns), power density of 50W/cm², and even with frequency of 10,000 Hz, motility increased and there was an absence of DNA damage. Probably, a positive result was obtained due to a small exposure time (30 seconds), and it was absent in normo- and asthenospermia, and was observed to be very significant (8.4 times), only with oligoasthenoteratozoospermia 30 minutes after laser illumination [114]. This confirms the well-known opinion that the degree of influence of LILI correlates with the severity of existing disorders (diabetes, neuropathy, etc.) [2]. There could not be a negative impact on DNA, even with such clearly overestimated energy parameters.
The absence of damage to the DNA of human spermatozoa has also been established for a continuous LILI of the red spectrum (wavelength 633 nm), even at a sufficiently high-power density (31 mW/cm²) the illumination was carried out for 30 minutes (!). Even more so, the motility of spermatozoa has increased insignificantly [120]. At the same time, it is known that the effect of LILI can effectively protect the reproductive system from external stress factors (immobilization stress by single binding of rats for 6 hours in the position on the back) [125, 126], as well as from the pathogenic effect of radiation (such as disorders of spermatogenesis in the form of partial blocking of the formation of mature spermatozoa from postmeiotic cells (spermatids) and the development of destructive processes at the cellular and subcellular levels) [127-129].

Negative effects on the reproductive system of male mice (decrease in the concentration and the activity of sperm dehydrogenases), while maintaining fertility, are manifested only after illumination 5 times a week continuously for 4 hours a day with completely prohibitive and unsafe parameters: wavelength 1064 nm, pulsed mode, power 5MW, light pulse duration 12 ns, frequency 12.5 Hz, pulse energy 0.03J, and average power 360 mW only after 35 days [130]. In other words, in order to damage the organism using laser light using correct parameters, you need to try very, very hard.

S.V. Goryunov (1995, 1996) [111, 112] unequivocally showed that the optimal exposure, for both the wavelength of LILI 633 nm (continuous mode) and for 890 nm (pulsed mode, pulse duration100 ns, power 5 mW), the optimal exposure at which the sperm motility, their oxidative activity and cellular metabolism increases (!). Even more so, the motility of spermatozoa has increased 4-5 times almost independently of the wavelength of the light source (470, 625, 660 and 850 nm) [113], and in studying the respiratory rate of spermatozoa of marine worms, a pronounced spectral dependence was observed in the wavelength range of 35-650 nm (maximum efficiency in the range of 400-430 nm) [44]. P. Gabel et al. (2009) [131] are convinced that the result is influenced by all exposure parameters: wavelength, power, exposure and coherence.

In the work of A.V. Stolyarov et al. (2002) [132], it was shown that artificial insemination of piglets with seed material after the preliminary illumination by LILI of different wavelengths (565, 595 and 660nm) allowed them to obtain the greatest increase in the number of pigs in the nest (+45%) at a wavelength of 595nm and exposure 0.5 min, and also good but less at 660 nm and one minute exposure (increase +25%).

We would also like to draw attention to the fact that all regularities were observed with direct exposure to spermatozoa in vitro, and when exposed to the patient's body, it is also necessary to take into account the anatomical features of the human body. Based on well-known generalized considerations, in particular, the understanding of biophysics of the processes of absorption and scattering of laser light, for clinical practice, the wavelength of 635 nm (red spectrum) is most often chosen when exposed to tissues and organs located at a depth of up to 5cm, and 890-904 nm (IR spectrum) when they are deeper (up to 15 cm) [2, 124].

The choice of spectral range data is also determined by the fact that it is in the regions of 600-650 nm and 850-900 nm, the absorption of light by spermatozoa is the most pronounced [111, 112].

5. Clinical studies

It should be noted that if the experimental studies on the influence of LILI of various in vitro and in vivo models which are somehow related to infertility are mostly by foreign authors, then clinical studies are performed almost exclusively by Russian scientists. Moreover, in Russia there is already very considerable practical experience of the use of laser therapy for these purposes.

In one of the few foreign clinical trials, the testes of men with oligozoospermia aged from 29 to 43 years old were illuminated with red continuous (633 nm, 12.5 mW) and pulsed infrared LILI (904 nm, a matrix of 5 laser diodes, a pulsed power of 12 W, frequency 800 Hz) for four minutes, twice a week, for only 10 sessions. Libido increased in 15 out of 20 patients alongside a significant improvement in the quality of sperm (increasing their motility and total number, reducing the number of abnormal ones) [133].

A.I. Gladkova (2011) [134] presented the results of her own multi-year experimental and clinical studies, as well as the work of her colleagues, which were used to substantiate the possibility of using laser therapy in andrology, showed the influence of various methods of laser influence on sexual behaviour, hormonal homeostasis, spermatogenesis and ability to fertilize [135-142].

Many researchers draw attention to the fact that the impact of pulsed infrared LILI with a transrectal delivery of laser light energy is preferable in the treatment of patients with chronic nonspecific prostatitis. Variation in frequency depending on the activity of the inflammatory process in the prostate gland allows to individualize therapy for patients with chronic obstructive pulmonary disease and to achieve better treatment results. LLLT in combination with traditional treatment is characterized by the more effective and rapid relief of the main symptoms of chronic obstructive pulmonary disease and a reduction in the frequency of complications [143-147]. The effect of traditional methods of treatment is intensified and potentiated through the generalization of the effect and the complex response of all homeostasis systems. The immuno-correcting action of LILI is caused by the stimulation of leukopoeza, including T-lymphocytes, which contributes to the rapid elimination of pathogens of urogenital infection. In this case, the number of patients with oligozoospermia after the treatment course decreases by more than 2-fold, and with asthenozoospermia with almost 4-fold [143-147]. In addition, laser action exerts a disaggregating effect on sperm, similar to the hypocoagulation effect of LILI on blood, which as a result improves the fertilizing properties of seminal fluid [19].

In another work, the laser therapeutic device with two infrared laser emitters (wavelength 890 nm, pulse power up to 10 W, 80 to 3000 Hz) was used. According to a method which based on the experience of other researchers using laser therapy, all patients underwent daily laser illumination on both testes simultaneously in the lateral and longitudinal projections for 10 days. This effect in the form of monotherapy with varicocele increases the concentration of active-mobile forms of spermatozoa from 25% to 37% and the number of morphologically normal forms from 27% to 39%. With idiopathic infertility, the use of local laser therapy causes an increase in sperm motility from 19% to 34% and an increase in the number of morphologically normal forms of spermatozoa from 13% to 23% [148-152].
This data is corroborated by the results of the studies, where the method was carried out in a similar manner, and the authors recommend that ligation of the spermatozoa by LILI prior to IVF is mandatory [153, 154]. Similar recommendations can be found in other works [105].

Clinical and experimental studies testify to the stimulating effect of LILI on the enhancement of the kinetic capabilities of spermatozoa and the functional-metabolic state of ejaculate neutrophils in patients with chlamydial infection, which can be used under appropriate clinical conditions [107-110].

For men of reproductive age who are in a partnership for more than one year, as well as those with symptoms of prostatitis, vesiculitis or epididymorchitis, it is necessary to conduct a clinical and microbiological examination to eliminate any hidden urogenital infections (chlamydia, trichomonias, mycoplasma genitalia, ureaplasma, herpes simplex virus, etc.) or sexually transmitted diseases, before the start of treatment, including an examination of all sexual partners. Laser therapy of patients with prostatitis and vesiculitis can eliminate infiltrative-exudative changes in the prostate gland, and the appointment depends on the stage of the inflammatory process in the prostate gland. Carrying out LLLT can improve the outflow of inflamed secretions from the glands of the prostate, increase local immunity, eliminate pain and dysuric symptoms and improve reproductive and copulatory functions [155, 156].

Since a direct link between the presence of epididymoortitis and infertility and the effectiveness of laser therapy in treating this category of patients is questionable [157-160], the inclusion of its complex recovery of male fertility is desirable.

A reliable large therapeutic effect that has positive, long-lasting lasting results in the treatment of infertility in men with chronic inflammatory diseases of the organs of reproduction is the use of IR LILI. The local effect on the fields of projection of the sexual glands is 91.7%, and the use of laser acupuncture is 85.2%, compared with traditional medicinal therapy, which is 76.8%. The local effect allows increasing the number of actively mobile sperm forms in the ejaculation by 45-50%, removing the inflammatory process and restoring microcirculation in the sex glands. Exposure to acupuncture points (AP) (Pat. 2185211 RU) [161] of the lumbar region further increases the concentration and reduces the number of pathological forms of sperm in the ejaculate by 10-15%, improving the endocrine regulation of spermatogenesis. At the same time, a sufficient therapeutic effect is achieved after 5 procedures. An additional course of LLLT is carried out 6-9 months after the main course [162-165].

A.B. Ikhayev (2013) [166] applied a combined-correlated method of laser therapy in patients with chronic nonspecific prostatitis with infertility in a strong and strongly-medium sexual constitution. A vibro-magneto-laser massage of the prostate gland [31] with the rectal attachment VMLG10 (LILI+magnetic field+ vibration) to the laser therapeutic device "Matrix-Urolog" (produced by Research Center Matrix, Russia) (wavelength 635 nm) every second day, five-minute exposure, laser illumination modulation frequency 10Hz, a course of 15 procedures. Patients with oligoasthenoteratozoospermia I-II stage with the duration of chronic abacterial prostatitis (CAP) up to 5 years and the age of up to 40 years, combined illumination therapy is also prescribed according to the method of local laser negative pressure (LLNP) [167; 168] for 12 minutes, every other day. This technique implies that a special flask with a laser head in the form of a ring is put on the penis. A vacuum (negative pressure) of 15-30 kPa is created and simultaneously lasers are illuminating. It repeats in cycles of 1.5 minutes. Under the influence of combined-correlated illumination therapy, the algic syndrome is stopped in 75%, dysuric syndrome in 61%, erectile dysfunction in 54% and asthenic-neurotic in 59.4% of patients. Normalized prostate gland size occurs in 80% and pituitary-adrenal-testicular system in 65% of patients with chronic prostatitis with infertility. The experience of clinical application of the proposed method of LLLLT for 12 months. showed that after the end of the treatment course, 67.5% of couples were pregnant [166].

High efficiency is also shown in intravenous laser illumination (ILBI) in the treatment of patients with CAP with impaired fertility. The Matrix-ILBI device (produced by Research Center Matrix, Russia), a wavelength of 635 nm, power of 1.5 mW at the output of KIVL-01 (intravenous light guides produced by Research Center Matrix, Russia), for a course of 10 sessions of 10 minutes. 15 patients (37.5%) were in a strong sexual constitution, 14 (35%) were in the middle and 11 (27.5%) were in a weak sexual constitution, a prostate massage was also performed daily (for a course of 15 procedures). As a result of the treatment, normospermia was detected in 72.5% patients with strong and medium sexual constitutions. As a result of the treatment, the concentration of follicle-stimulating hormone (FSH) in the blood decreased by 28%, luteinizing hormone by 17%, estradiol by 17%, prolactin (PRL) by 38%, dehydroepiandrosterone sulfate - by 18%, testosterone - increased by 33.5%, taking the regulatory data (p > 0.05). As a result of treatment, the functional activity of the hypothalamic-pituitary-adrenal-testicular system occurred in 27 (67.5%) patients with a duration of CAP no more than 5 years. Within one year after the course of treatment, pregnancy occurred in 25 (62.5%) partnered couples in which men were between the ages of 22 and 40 with a strong and medium sexual constitution, with a duration of CAP ≤ 5 years [169-171].

With the main treatment regimens, it is recommended to perform laser acupuncture, the effect of LILI on AP of the lumbar region and balneoacupuncture (iodine-bromine baths) to improve efficacy [168, 172-175].

Based on these studies in Roszdravnadzor, a complex method of the correction of infertility in patients with chronic prostatitis was recorded [176].

Patients with reproductive dysfunction alongside even abacterial prostatitis are advised to use ultraviolet blood illumination (UVBI), which is more often used for various disorders of the immune system [29, 177, 178]. Currently, the LUVBI® (laser ultraviolet blood illumination) technique is done intravenously, using only LILI with a wavelength in the range of 365-405 nm and almost always combining every other day with ILBI-635 (wavelength 635 nm, power is 1-2 mW) [179].

If the hormonal function and spermatogenesis are impaired in men with obesity of no more than 2 grade, it is advisable to prescribe a combined treatment that includes the action of pulsed infrared LILI (890-904 nm) on the collar area (projection of the vertebral arteries at the C3-C7 level and the subcapsular region according to the labile technique, scanning with a speed of 1cm/s) and other physiotherapy methods alongside a standard complex (low-calorie diet, moderate exercise and long-term pharmacotherapy). In case of the violation of the copulatory function, it is advisable to prescribe to patients also a local effect on the testicles (in the lateral and longitudinal projections, 5 minutes for each testicle) and rectal fillings of pantocrine [180-182].

Regarding Slonimskiy B.Yu. [181], a complex treatment program in patients with obesity and impaired fertility can eliminate lipid imbalance, normalize some metabolic parameters, including
Given in table form (Table 3).

Publications are publicly available, only the main provisions related to fertility, in which LILI is used. Since the full text of all papers was not accessible, it was possible to identify nine patents, to some extent, describing the influence of LILI on Sertoli cells [149, 183].

Spermatozoa from 11.5 mU/ml to 8.0 mU/ml, which indirectly indicated the decrease in FSH levels in patients with severe oligoasthenoteratozoospermia [181].

It is necessary to use the available low level laser therapy methods as widely as possible: local, rectal, laser acupuncture, ILBI, on the projection of various organs, paravertebrally, etc., while setting all parameters of the laser (wavelength, mode of operation, frequency for pulsed lasers, power, density power determined by the method of exposure, exposure, localization), which are established by appropriate regulatory documents and clinical recommendations [3, 193].

6. Conclusion

Despite the active debates and discussions on the topic of the presence/absence of "full-fledged" diagnostics, the case of idiopathic sperm quality disorders in more than half of the cases of male infertility is unquestionable. Consequently, in the first place clinicians should consider the non-specific treatment methods aimed at "general improvement" that trigger the mechanisms of sanogenesis, restoration of disturbed homeostasis and normal physiological regulation.

Previously, it was thought that laser therapy was only of an auxiliary nature and is prescribed in conjunction with drug therapy or at the final stage of traditional treatment [192], but further studies completely refute this view. Analysis of the scientific literature suggests that laser therapy should be used as much as possible in the complex treatment of men with infertility, since the effectiveness of the method is not just high, but often has no alternatives. For laser illumination, it is best to use exclusively pulsed LILI, red (635 nm) and infrared (904 nm) for local illumination, alternating with continuous LILI with a wavelength of 635 nm (red spectrum) and 365 nm (ultraviolet) for intravaginal laser blood illumination.

It is necessary to use the available low level laser therapy methods as widely as possible: local, rectal, laser acupuncture, ILBI, on the projection of various organs, paravertebrally, etc., while setting all parameters of the laser (wavelength, mode of operation, frequency for pulsed lasers, power, density power determined by the method of exposure, exposure, localization), which are established by appropriate regulatory documents and clinical recommendations [3, 193].

Open Access This article is distributed under terms of the Creative Commons Attribution License which permits any use, distribution, and reproduction in any medium, provided original author(s) and source are credited.

Table 3 − Patents in which LILI illumination is associated with various aspects of infertility.

| Purpose, goal | Laser exposure parameters | Impact localization, method | Patent |
|---------------|---------------------------|-----------------------------|--------|
| Improving the quality of sperm production in male boars | Not specified | 3 AP (acupuncture points) with localization description | [183] |
| Treatment of men with the pathology of spermatogenesis | 635 nm, continuous mode, 3-4mW | Corporal AP: T3, T4, V23 + one of the auricular: AP22, AP23, AP32 | [184] |
| Treatment of men with autoimmune infertility | 365-400 nm, 20 mW (incoherent light), 30 minutes, 6 daily procedures | UVBI intravenously | [161] |
| Improvement of sperm quality in pathospermia in the IVF program | Pulsed infrared IR LILI, 890 nm, 3.5 W, 300-600 Hz, 7-10 minutes, 5-7 daily procedures | On the perineum and suprapubic region | [186] |
| Treatment of men with autoimmune infertility | 660 nm, light-emitting diodes, modulated mode, frequency 1-5 Hz, 1 mW/cm², 15-20 minutes with pauses, 10 daily procedures | The penis, LNP (local negative pressure + incoherent illumination) | [187] |
| Stimulation of spermatogenesis | 635 nm, continuous operation, 30 mW, 10-15 daily procedures | Contact on the area of the scrotum | [188] |
| Treatment of men with impaired spermatogenesis | Not specified | UVBI | [189] |
| Stimulation of spermatogenesis in the experiment, non-native male rats | 475 nm, continuous mode, 10 mW/cm², 1 minute, 10 daily sessions | On the testicles | [190] |
| Increase in the functional and metabolic status of human spermatozoa | 635 nm, modulated mode, frequency 100 Hz, 10 mW/cm², 1 minute | Spermatozoa derived from healthy human semen in vitro | [191] |
REFERENCES

[1] Marincola FM. Translational medicine: a two-way road. J Transl Med. 2003; 1: 1-2.

[2] Moskvin SV. The effectiveness of laser therapy. Series “Effective laser therapy”. Moscow, Tver’. Triada. 2012.

[3] Gerasimenko MYu, Geynits AV, Moskvin SV, Astakhov PV, Babushkina GV, Gushchina, et al. Laser therapy in medical rehabilitation and prevention programs: clinical guidelines. FSBI "Russian Scientific Center for Medical Rehabilitation and Balneology" Ministry of Health of Russia, FSBI "State Scientific Center of Laser Medicine of FMBA of Russia". Moscow, 2015.

[4] Bozhedomov VA, Rokhlakov IM, Tretyakov AA, Lipatova NA, Vinogradov IV. Andrologic aspects of infertile marriage. Meditsinskii sovet. 2013; 8: 13-7.

[5] Ol’ D, Shaster T, Kvolich S. Male infertility. In: Fal’kone T, Kherd V, eds. Reproductive medicine and surgery. 2010.

[6] Jungwirth A, Diemer T, Dohle GR, Giwercman A, Kopa Z, Krausz et al. Male infertility. In: Fal’kone T, Gerasimenko MYu, Geynits AV, Moskvin SV, Astahkov PV, Ba -

[7] WHO Manual for the Standardized Investigation, Diagnosis and Management of the Infertile Male. Cambridge: Cambridge University Press. 2000; 91.

[8] Shcheplev PA, Apolikhin Ol. Male infertility. Consensus discussion. Bull of Reprod Health. 2010; 3-4: 37-44.

[9] Nuti F, Krausz C. Gene polymorphisms/mutations relevant to abnormal spermatogenesis. Reprod. Biomed. Online 2008; 16(4): 504-13.

[10] Miktadova AV, Mashkina EV, Volosovtscova GI, Koygerova ES, Moskvin SV, Khadartsev AA. Laser light - it can harm them? (literature review). J New Med Technol. 2008; 15(1): 226-83.

[11] Al-Shukri SH, Kuzmin IV, Slesarevskaya MN, Sokolov AV. The effect of low-intensity laser radiation on semen parameters in patients with chronic prostatitis. Urolog vedom. 2015; 5(4): 8-12.

[12] Balter RB, Mikhailov DV, Ivanova TV. Infertile marriage. Samara, 2015.

[13] Zhiborev BN. Varicocele and male sterility in view of polygenic hypogonadism nature and the manifestation of dysplasia syndrome of the connective tissue. Rossiiisky mediko-biologicheskiy vestnik im. akademika I.P. Pavlova. 2007; 4: 72-9.

[14] Condorelli RA, Russo GI, Calogero AE, Morgia G, La Vignera S. Chronic prostatitis and its detrimental impact on sperm parameters: a systematic review and meta-analysis. J Endocrinol Invest. 2017; 40(11): 1209-18. doi: 10.1007/s40618-017-0684-0.

[15] Giamarellou H, Tympanidis R, Bitos N, Leonidas E, Daikos GK. Infertility and chronic prostatitis. Andrologia. 1984; 16(5): 417-22.

[16] Pavlova ZSh, Kalinchenko SYu, Kamalov AA, Tishova YuA, Zhuykov AV, Gusakova DA, et al. Vitamin D deficiency and male infertility actual problems of the 21st century: male infertility, obesity and vitamin D - is there a relationship? Vest Ural Med Akadem Nauki. 2013; 3(45): 26-32.

[17] Tuyuzikov IA. Metabolic syndrome and male infertility (review). Androl Gen Surg. 2013; 2: 5-10.

[18] Arno’di EK. Chronic prostatitis: problems, experience, prospects. Rostov-na-Donu, 1999.

[19] Imshinetskaya LP. The role of hormonal changes in the pathogenesis of sexual disorders and infertility in chronic nonspecific prostatitis [Abstract of the thesis]. Kiev, 1983.

[20] Mikhaylichenko VV. Pathogenesis, clinic, diagnosis and treatment of copulative and reproductive disorders in men with congestion in the genitourinary venous plexus [Abstract of the thesis]. Saint Petersburg, 1996.

[21] Satybaldyev ShR. Medical rehabilitation of patients with chronic prostatitis with reproductive dysfunction [Abstract of the thesis]. Bishkek, 2000.

[22] Fedorova TA, Moskvin SV, Apolikhina IA. Laser therapy in obstetrics and gynecology. Moscow-Tver’. Triada, 2009.

[23] Ivanchenko LP, Kozidoba AS, Moskvin SV. Laser therapy in urology. Moscow-Tver’. Triada, 2009.

[24] Moskvin SV, Gorbani NA. Laser-vacuum massage. Moscow-Tver’. Triada, 2010.

[25] Moskvin SV, Geynits AV, Kochetkov AV, Gorbani NA, Ryazanova EA, et al. Laser-vacuum massage LAZMIK in medicine and cosmetology. Moscow-Tver’. Triada, 2014.

[26] Moskvin SV. About mechanism of therapeutic influence of low-frequency laser radiation. J New Med Technol. 2008; 15(1): 167-72.

[27] Goldstein SF. Irradiation of sperm tails by laser microbeam. J Exp Biol. 1969; 51(2): 431-41.

[28] Adamkovskaya MV. Influence of temperament, behavioral characteristics and other factors on the reproductive qualities of stallions: [Abstract of the thesis]. Divovo, 2004.

[29] Pataraya LM, Chelidze PV, Chichinadze NK. Influence of laser radiation on the ultrastructure of the testis of rats. In: Endocrinology and hormone receptors in reproduction. Tbilisi, 2004.

[30] Pataraya LM, Chelidze PV, Chichinadze NK. Influence of laser radiation on the ultrastructure of the testis of rats. In: Endocrinology and hormone receptors in reproduction. Tbilisi, 2004.

[31] Pataraya LM, Chelidze PV, Chichinadze NK. Influence of laser radiation on the ultrastructure of the testis of rats. In: Endocrinology and hormone receptors in reproduction. Tbilisi, 2004.
Lubart R, Shainberg A, Eichler M. Increased ATP levels in cardiac spermatoozoa motility is dependent on laser output power. Lasers Med Sci. 2009; 24(5): 703-13.

Lubart R, Rivera MM, Rigau T, Rodriguez-Gil JE, Rigau J. The effect of low level laser irradiation on sperm motility is dependent on power laser application. Abstracts from 7th International Congress of the World Association for Laser Therapy, 2008. Photomed Laser Surg. 2009; 27(1):186.

Dreyer TR, Siquest ND, Magrini PA, Fiorito PA, Assumpção MEOA, Nichi Met, et al. Biochemical and topological analysis of bovine sperm cells induced by low power laser irradiation. Medical Laser Applications and Laser-Tissue Interactions: Proceedings of SPIE-OSA Biomedical Optics, SPIE, 2011, 8092, 80920V. doi: 10.1117/12.890017

Drozdov AL, Karu TI, Chudnovskii VM, Yusupov VI, Bagratashvili VN. Influence of low-intensity red laser and diode laser on the locomotor activity of sea urchin sperm. Dokl Biochem Biophys. 2014; 457(1): 146-8. doi: 10.1134/s1607672914040085.

Fujiiwara A, Tazawa E, Yasumasa I. Activating effect of light irradiation at various wavelength on the respiration in sperm of the echinoid, Urechis unicinctus, in the presence of carbon monoxide. J Biochem. 1991; 109(3): 486-91.

Iaffaldano N, Rosato MP, Paventi G, Pizzuro R, Gambacorta M, Manchisi A, et al. The irradiation of rabbit sperm cells with He–Ne laser prevents their in vitro liquid storage dependent damage. Anim Reprod Sci. 2010; 119: 123-9. doi: 10.1016/j.anireprosci.2009.10.005

Iaffaldano N, Paventi G, Pizzuro R, Passarella S, Cerolini S, Zanini L, et al. The post-thaw irradiation of avian spermatozoa with He–Ne laser differently affects chicken, pheasant and turkey sperm quality. Anim Reprod Sci. 2013; 142(3-4):168-72. doi: 10.1016/j.anireprosci.2013.09.010.

Lubart R, Friedmann H, Levinthal T, Lavi R, Breitbart H. Effect of light on calcium transport in bull sperm cells. J Photochem Photobiol B: Biology. 1992; 15(4): 337-41.

Lubart R, Levinthal T, Cohen N, Friedmann H, Breitbart H. Changes in calcium transport in mammalian sperm mitochondria and plasma membrane due to 633 nm and 780 nm irradiation. In: Hofstetter A, Waidelich W, Staehler G, Waidelich R, eds. Laser in Medicine (Laser in Medicine). Berlin Heidelberg: Springer-Verlag. 1996; 449-53. doi: 10.1007/978-3-642-80264-5_107

Lubart R, Friedmann H, Sinyakov M, Cohen N, Breitbart H. Changes in calcium transport in mammalian sperm mitochondria and plasma membranes caused by 780 nm irradiation. Lasers Surg Med. 1997; 21(5): 493-9.

Lubart R, Shainberg A, Eichler M. Increased ATP levels in cardiac and sperm cells immediately after broadband visible light illumination. 27th International Congress Laser Medicine & IALMS Courses jointed with W.H.A. World Health Academy “Laser Florence 2013”. Lasers Med Sci. 2013; 28(6): 1415-6.

Marin ML, Velez JR. Efectos de la irradiation laser heli+neon en semen bovino [Tesis]. 1980: 19-90.

Salman Yazdi R, Bakhshi S, Jannat Alipoor F, Akhoond MR, Ansary A. Effect of 830-nm diode laser irradiation on human sperm motility. Int J Fertility Sterility. 2010; 4(Suppl 1): 31-2.

Salman Yazdi R, Bakhshi S, Jannat Alipoor F, Akhoond MR, Borhani S, Farrahi F, et al. Effect of 830-nm diode laser irradiation on human sperm motility. Lasers Med Sci. 2014; 29(1): 97-104. doi: 10.1007/s10103-013-1276-7.

Sato H. Efectos de la luz laser sobre la movilidad y la velocidad de esperma in vitro. Invest Clin Laser. 1986; 3: 80.

Sato H, Landthaler M, Haina D, Schill WB. The effects of laser light on sperm motility and velocity in vitro. Andrologia. 1984; 16(1): 23-5.

Siqueira AFP, Maria FS, Mendes CM, Hamilton TR, Dalmazzo A, Dreyer TR, et al. Effects of photobiomodulation therapy (PBMT) on bovine sperm function. Lasers Med Sci. 2016; 31(6): 1245-50.

Wenbin Y, Wenzhong L, Mengzhao L, Baotian Z, Laizeng AI, Tongya L, et al. Effects of laser radiation on Saanen buck’s sperm energy metabolism. Proceedings of the Sixth International Conference on Goats. Beijing, China; 1996.

Zan-Bar T, Bartooov B, Segal R, Yehuda R, Lavi R, Lubart R et al. Influence of visible light and ultraviolet irradiation on motility and fertility of mammalian and fish sperm. Photomed Laser Surg. 2005; 23(6): 549-55.

Shkuratov DYu, Chudnovskiy VM, Drozdov AL. The influence of low intensity laser radiation and superfhigh-frequency electromagnetic fields on gametes of marine invertebrates. Tsitologiya. 1997; 39(1): 25-8.

Lisichenko NL, Romodanova EA, Nardid OA, Dyubko TS, Roshal’ AD. Structural changes in the components of boar semen under the influence of small doses of laser irradiation. Fotobiol Fotomed. 2000; 3(3-4): 86.

Amaroli A, Gambardella C, Ferrando S, Hanna R, Benedicenti A, Gallus L, et al. The effect of photobiomodulation on the sea urchin paracentrotus lividus (echinodermata) using higher-fluence on fertilization, embryogenesis, and larval development: an in vitro study. Photomed Laser Surg. 2017; 35(3):127-35. doi: 10.1089/pho.2016.4136

Alexandratou E, Yova D, Handris P, Kletsas D, Loukas S. Human fibroblast alterations induced by low power laser irradiation at the single cell level using confocal microscopy. Photochem Photobiol Sci. 2002; 1(8):547-52.

Aloyan KA, Matveev AV, Morev VV, Kornev IA. Physiology of sperm motility. Urolog Vedom. 2013; 3(4):14-9.

Ruiz-Pesini E, Diez C, Lapeña AC, Perez-Martios A, Montoya J, Alvarez E, et al. Correlation of sperm motility with mitochondrial enzymatic activities. Clin Chem. 1998; 44(8 Pt 1):1616-20.

Rossato M, Di Virgilio F, Rizzuto R, Galeazzi C, Foresta C. Intra-cellular calcium store depletion and acrosome reaction in human spermatozoa: role of calcium and plasma membrane potential. Mol Hum Reprod. 2001; 7(2):119-28.

Ankri R, Friedman H, Savion N, Kotev-Emeth S, Breitbart H, Lubart R. Visible light induces no formation in sperm and endothelial cells. Lasers Surg Med. 2010; 42(4):348-52.

Porras MD, Bermudez D, Parrado C. Effects biologicos de la radiation laser IR sobre el epitelio seminifero. Invest Clin Laser. 1984; 3(1): 57-60.

Celani MF, Gilioli G, Fano AR. The effect of laser radiation on Leydig cells: Functional and morphological studies. IRCS Med Sci. 1984; 12 (9): 883-4.
Celani MF, Gilioli G, Montanini V, Morrama P. Further evidence that mid laser radiations may stimulate Leydig cell steroidogenesis. IRCS Med Sci. 1985; 13(4): 336-7.

Celani MF, Grandi M, Gilioli G. Changes in mouse Leydig cell steroidogenesis following infrared and helium–neon laser irradiation. Exp Clin Endocrinol. 1987; 80(1): 16-22.

Taha MA, Valojerdi MR. Quantitative and qualitative changes of the seminiferous epithelium induced by Ga. Al. As. (830 nm) laser radiation. Lasers Surg Med. 2004; 34(4): 352-9.

Alves MB, de Arruda RP, Batissaco L, Florez-Rodriguez SA, de Oliveira BM, Torres MA, et al. Low-level laser therapy to recovery testicular degeneration in rams: effects on seminal characteristics, scrotal temperature, plasma testosterone concentration, and testes histopathology. Lasers Med Sci. 2016; 31(3): 695-704.

Au DW, Chiang MW, Tang JY, Yuen BB, Wang YL, Wu RS. Impairment of sea urchin sperm quality by UV-B radiation: predicting fertilization success from sperm motility. Mar Pollut Bull. 2002; 44(7): 583-9.

Breitbart H, Wehbie R, Lardy H. Regulation of calcium transport in bovine spermatozoa. Biochim Biophys Acta. 1990; 1027(1):72-8.

Breitbart H, Wehbie RS, Lardy H. Calcium transport in bovine sperm mitochondria: Effect of substrates and phosphate. Biochim Biophys Acta. 1990; 1026(1): 57-63.

Breitbart H, Levinshal T, Cohen N, Friedmann H, Lubart R, et al. Changes in calcium transport in mammalian sperm mitochondria and plasma membrane irradiated at 633 nm (HeNe laser). J Photochem Photobiol B. 1996; 34(2-3):117-21.

Cohen N, Lubart R, Rubinstein S, Breitbart H. Light irradiation of mouse spermatozoa: stimulation of in vitro fertilization and calcium signals. Photochem Photobiol. 1998; 68(3): 407-13.

Lubart R, Breitbart H, Sofer Y, Lavi R. He-Ne irradiation of human spermatozoa: enhancement in hamster egg penetration. Laser Ther. 1999; 11(4): 171-6.

Lubart R, Breitbart H, Sofer Y, Cohen N, Friedmann H, Bouskila E, et al. Light irradiation of sperm cells stimulates in vitro fertilization. 20th Intern Congress "Laser Florence 2005". Florence. 2005: S18-S19.

Lubart R, Eichler M., Lavi R., Shainberg A. Flavins are source of low energy visible light-induced oxy radicals formation in cells. 20th Intern Congress "Laser Florence 2005". Florence. 2005: S21.

Lubart R, Breitbart H, Lavi R. Photobiostimulation as a function of different wavelengths. Laser Ther. 2000; 12(1): 38-41.

Lubart R, Shainberg A, Lavi R. EPR spectroscopy of 1O2 reveals enhanced redox activity in low power laser illuminated cell cultures. 15th World Congress of the ISLSMS. Munich, 2003: 155.

Lavi R., Sinyakov M., Eichler M., Isaac A., Zinnman T., Shainberg A., et al. Generation of reactive oxygen species and free electrons in visible light illuminated plasma membranes. 20th Intern Congress “Laser Florence 2005”. Florence. 2005: S18.

Lavi R, Shainberg A, Shneyveys V, Hochauer E, Isaac A, Zinnman T, et al. Detailed analysis of reactive oxygen species induced by visible light in various cell types. Lasers Surg Med. 2010; 42(6): 473-80.

Shahar S., Wiser A., Ickowicz D., Lubart R., Shulman A., Breitbart H. Light-mediated activation reveals a key role for protein kinase A and sarcoma protein kinase in the development of sperm hyper-activated motility. Hum Reprod. 2011; 26 (9): 2274-82. doi: 10.1093/humrep/der232.

Meier B., Cross A.R., Hancock J.T., Kaup FJ, Jones OT. Identification of a superoxide-generating NADPH oxidase system in human fibroblasts. Biochem J. 1991, 275(1): 241-5.

Pal G., Dutta A., Mitra K, Grace MS, Romanycz KB, et al. Effect of low intensity laser interaction with human skin fibroblast cells using fiber-optic nano-probes. J Photochem Photobiol B. 2007, 86(3): 252-61.

Suzuki K.-J., Nakaji S., Kogawa T, Kumeta K, Oka E, Kitagawa N, et al. Mechanistic approach to the effects of low level laser irradiation (LLLI) with the GaAlAs diode laser on the production of reactive oxygen species from human neutrophils as a model for therapeutic modality at a cellular level. Laser Ther. 2005, 14(2): 75-81.

Takahashi J., Umeda T., Oyama T, Shimaya S, Yaegaki M, Matsuzaka M, et al. Effects of low incident levels of laser irradiation and other environmental factors on the production capability of reactive oxygen species from human neutrophils. Laser Ther. 2005, 14(2): 55-65.

Doblin N, Zamfirescu S, Anghel AH, Topoleanu I, Nicolaia I, Gianluca P, et al. Study on the effects of exposure to different doses of energy generated by a He-Ne laser on the quality of frozen-thawed semen of ram. Rom Biotechn Lett. 2015; 20(3): 10381-7.

Fernandes GHC, de Carvalho Pde T, Serra AJ, Crespilho AM, Peron JP, Rossato C, et al. The effect of low-level laser irradiation on sperm motility, and integrity of the plasma membrane and acrosome in cryopreserved bovine sperm. PLoS One. 2015; 10(3): e0121487. doi: 10.1371/journal.pone.0121487.

Iaffaldano N, Meluzzi A, Manchisi A, Passarella S. Improvement of stored turkey semen quality as a result of He–Ne laser irradiation. Anim Reprod Sci. 2005; 85(3-4): 317-25.

Ocaña-Quero JM, Gomez-Villamandos R, Moreno-Millan M, Santisteban-Valenzuela JM. Biological effects of helium-neon (He-Ne) laser irradiation on acrosome reaction in bull sperm cells. J Photochem Photobiol B. 1997; 40(3): 294-8.

Yeste M, Codony F, Estrada E, Lleonart M, Balasch S, Peña A, et al. Specific LED-based red light photo-stimulation procedures improve overall sperm function and reproductive performance of boar ejaculates. Sci Rep. 2016; 6:22569. doi: 10.1038/srep22569.

Ocaña Quero JM, Gomez Villamandos RJ, Moreno-Millan M, Santisteban Valenzuela JM. The effect of helium-neon laser irradiation on in vitro maturation and fertilization of immature bovine oocytes. Lasers Med Sci. 1995; 10(2): 113-9.

Bielskis A, Hare WCD. Development in vitro of bovine embryos after exposure to continuous helium-neon laser light. Theriogenology. 1992; 37:192.

Hirao Y, Yanagimachi R. Detrimental effect of visible light on meiosis of mammalian eggs in vitro. J Exp Zool. 1978; 206(3): 365-70.

Levi AC, Pettro R, Sicardi E. Laser irradiation on chicken embryos. Boll Soc Ital Biol Sper. 1987; 3(4): 233-6.

Moreno-Millan M, Ocaña-Quero JM. Preliminary results of the evaluation of the use of clinical laser He–Ne radiation in the process of bovine “in vitro fertilization”. Bulletin UASVM Vet Med. 2009; 66: 495.

Ocaña-Quero JM, Gomez Villamandos R, Moreno Millan M, Santisteban Valenzuela JM. The effect of the Helium-Neon laser radia-
The effect of the low-level laser irradiation in bovine embryo production system. J Biomed Opt. 2014; 19(3): 035006-9. doi:10.1117/1.JBO.19.3.035006

Mims MF, McKinnell RG. Laser irradiation of the chick embryo germinal crescent. J Embryol Exp Morph. 1971; 26(1): 31-6.

Whitaker M, Smith J. Introduction. Calcium signals and developmental patterning. Philos Trans R Soc Lond B Biol Sci. 2008; 363(1495): 1307-10. doi: 10.1098/rstb.2007.2248.

Jaffe LF. Sources of calcium in egg activation: a review and hypothesis. Dev Biol. 1983; 99(2): 265-76.

Jaffe LF. Calcium waves. Phil Trans R Soc B. 2012; 363: 1311-6. doi:10.1098/rstb.2007.2249

Gizinger OA, Frantseva OV. Low-intensity laser therapy in correction of motor dysfunction of spermatozoa in patients with urogenital infections. Yuzh Ural Med Zhurn. 2014; 3: 35-41.

Gizinger OA, Frantseva OV, Zabirova MR. The effect of exposure of sperm and studying the effects of this effect on human spermatozoa (experimental study). Proceedings of "Appl of Lasers in Biol and Med". 1995: 120-1.

Goryunov SV. Influence of low-energy laser radiation on human spermatozoa (experimental study) [Abstract of the thesis]. Moscow; 1996.

Ban Frangez H, Frangez I, Verdenik I, Jansa V, Virant Klun I. Long-term low-power laser radiation on the generative function of Leydig cells under the influence of drinking mineral water and electromagnetic radiation under the stress conditions in the rats. Voprosy Kurortol Fizioter Lech Fiz Kult. 2016; 5: 43-6.

Korolev YuN, Nikulina LA. The ultrastructure of Leydig cells under the influence of drinking mineral water and electromagnetic radiation under the stress conditions in the rats. Voprosy Kurortol Fizioter Lech Fiz Kult. 2016; 5: 37-41.

Korolev YuN, Bobrovnitsky IP, Geniatulina MS, et al. The combined action of drinking mineral water and low-intensity electromagnetic radiation under the immobilization stress conditions (an experimental study). Voprosy Kurortol Fizioter Lech Fiz Kult. 2015; 6: 37-41.

Korolev YuN, Mikhailik LV, Geniatulina MS, Nikulina LA. The use of drinkable sulfate mineral water in combination with laser and magnetolaser irradiation for primary prophylaxis of post-radiation problems (experimental study). Voprosy Kurortol Fizioter Lech Fiz Kult. 2010; 4:3-6.

Korolev YuN, Kurilo LF, Geniatulina MS, Nikulina L. A., Makarova N. P. The radioprotective effect of laser radiation on the spermatogenesis of rats and their progeny. Probl Reprod. 2007; 1: 34-7.

Makarova NP, Korolev UN, Kurilo LF, Shileyko L.V., Ostroumova T. V., Nikulina L. A., et al. Effect of low intensity laser radiation on testicular tissue during common ionizing irradiation. Androlog Gen Surg. 2005; 1: 23-5.

Berezinskaya AN, Mendel'son GI, Makarova IV. The influence of long-term low-power laser radiation on the generative function of male mice. Gigiyen Aspekt Ispol Lazer Izluch Narod Khoz. Moscow: 1982: 143-4.

Gabel P, Harrison K, Sherrin D, Carroll J. Sperm motility enhancement with low level laser and led photobiomodulation. A dose response study. Abstracts from 7th International Congress of the World Association for Laser Therapy; 2008. Photomed Laser Surg. 2009; 27(1): 160.

Stolyarov AV, Lisichenko HL, Grabina VA. The effect of exposure and wavelength on the efficiency of reproduction in the processes of laser sperm treatment. Proceedings of the XVIII International Scientific-Practical Conference "The use of lasers in medicine and biology." Yalta; 2002: 64-5.
of local negative pressure and laser illumination. Urologiya. 2014; 3: 48-53.

[169] Putilin VA. Endovascular laser and balneotherapy combined with laser acupuncture in complex treatment of infertility in patients with chronic prostatitis. [Abstract of the thesis]. Pyatigorsk, 2009.

[170] Tereshin AT, Putilin VA, Mashnin VV, Morozov FA. Laser-therapy of fertile disturbances in patients with chronic prostatitis. J New Med Technol. 2007; 14(4): 208.

[171] Tereshin AT, Putilin VA, Mashnin VV, Morozov FA. Laserotherapy at disorders of fertility in the patients with chronic prostatitis. J New Med Technol. 2008; 15(4): 121.

[172] Agaev AA. The use of acu- and laser puncture in combination with balneo and peloid therapy in men with impaired fertility caused by nonspecific inflammatory diseases of the genital organs. [Thesis]. Pytigorsk, 1998.

[173] Ikhayev AB, Teroshin AT. Laser therapy, acu- and laser puncture in correction of infertility in patients with chronic prostatitis. Proceedings of the VII Intern Congress PAAR. Sochi, 2012.

[174] Tereshin AT, Istoshin NG, Putilin VA, Merslikin NV. Combined use of the laserotherapy, acu- and laseropuncture in correction of infertility in patients with chronic prostatitis. J New Med Technol. 2008; 15(4): 158-60.

[175] Tereshin AT, Istoshin NG, Putilin VA, Mashnin VV. Balneo-, laser-therapy, acu- and laseropuncture in correction in infertility in patients with chronic prostatitis. J New Med Technol. 2009; 16(1): 74-7.

[176] New medical technology FS № 2008/234 from 07.11.2008. Combined use of endovascular laser therapy, acu- and laser puncture in correction of infertility in patients with chronic prostatitis / Pyatigorsk State Scientific Research Institute of Balneology. Moscow, 2008.

[177] Satybaldiev ShR, Satybaldiyev ESh, Evdokimov VV. Rehabilitation reproductive function in patients in official infertile marriages. Androlog Gen Surg. 2013; 14(4): 69-72.

[178] Satibalidiyev ShR, Satibalidiyev ESh, Evdokimov VV. Treatment of the patients with chronic abacterial prostatitis and fertility disturbances. Exper Clin Urol. 2014; 4: 43-6.

[179] Moskvin SV, Borisova ON, Belyaeva EA. Intravenous laser blood fluorering. Klin Med Farmak. 2017; 3(1): 21-5.

[180] Slonimskiy BYu. Features of the blood supply to the penis in the patients with obesity and reproductive dysfunction at the use of the developed complex program and its individual components. J New Med Technol. eEdition. 2013; 1: 155.

[181] Slonimskiy BYu. Modern programs for the restoration of reproductive function in obese men. [Abstract of the thesis]. Moscow, 2013.

[182] Slonimskiy BYu, Kotenko KV, Schukin AI. Innovative technologies of vegetative correction in the treatment of patients with obesity and reproductive dysfunction. J New Med Technol. eEdition. 2013; 1: 156.

[183] Mufaged ML, Tirsi KA, Siluyanov KA, Novitskiy VYe. Application of low-intensity laser irradiation in the treatment of infertile patients with varicocele. Vest Ross Gos Univ. (special issue) 2004; 2(33): 17.

[184] Sheyko IP, Gorbunov YuA, Budevich AI, Yeliseykin DV. Method for improving the quality of sperm production in breeding boars. Patent 8413 BY, 30.09.2003.

[185] Chayka VK, Kvaschenko VP, Ostapenko OI. Method for treating patients with pathology of spermatogenesis Patent 62075 UA, 15.12.2003.

[186] Gavrilev YuA, Kaz'michev LN, Leonov BV, Levchuk TN. Method for improving sperm quality in the cases of pathospermia applicable in artificial fertilization program. Patent 2205047 RU, 27.05.2003.

[187] Kaliina SN, Tikistskii OL, Aleksandrov VP, Sajdullov L, Mishanin EA. Method for treating autoimmune male infertility cases. Patent 2294779 RU, 10.03.2007.

[188] Chekmarev VM, Kharchenko IV, Mashkov AE. Method of complex spermatogenesis stimulation. Patent 2406549 RU, 20.12.2010.

[189] Zagarskikh EYu, Kolesnikova LI, Dolgikh VV, Kolesnikov SI, Zagarskikh AYu, Kurashova NA, et al. Application of musk deer musk tincture and ultraviolet irradiation of blood for treatment of spermatogenic failure in men of reproductive age. Patent 2418581 RU, 20.05.2011.

[190] Shcherbatsyuk TG, Novikova YaS, Chernov VV.Method of experimental stimulation of spermatogenesis. Patent 2481132 RU, 10.05.2013.

[191] Gizinger OA, Dolgushin II, Frantseva OV, Kurenkov EL. Method of increasing functional-metabolic status of sperm cells obtained from semen of healthy individual in vitro under effect of low-intensity laser. Patent 2583949 RU, 10.05.2016.

[192] Avdoshin VP, Pershin KB, Krutov IV. Magnetic laser therapy for chronic prostatitis. Proceedings of the Plenum of the All-Russian Society of Urology. Perm’. 1994: 12-3.

[193] Moskvin SV, Kisleiev SB. Laser therapy for joint and muscle pain. Moscow–Tver: "Triada". 2017.