The Application of Different Lasers in Treatment of Male and Female Infertility: A Review

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ABSTRACT

One of the main worldwide health burdens that couples are facing is infertility. The reasons leading into infertility are attributed equally to males and females. The first usage of laser for the treatment of infertility was in the 1980s, followed by a rapidly growing application in medicine. A variety of biological processes is triggered by laser therapy through interaction with primary cellular photoacceptors. The application of laser in the IVF/ICSI process is increasingly attracting interest. Also, using lasers for assisted hatching has been developed to more accurately control the opening procedure of the zona and facilitates implantation of embryo after being transferred into the uterus. For the first time, the clinical application of different lasers was reviewed based on parameters such as: the quality of sperm and oocyte in ART, sperm properties and different types of diseases. In this review, the indications, limitations, advantages, outcomes, safety and implication of lasers were highlighted for male and female factor infertility aiming to improve, and more judicious use of laser therapy and maximize its potential benefits while minimizing some foreseen complications.

Keywords: Infertility; Assisted Reproductive Technology; Lasers; Sperm; Oocyte.

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Introduction

Nowadays, infertility affects 10-15 percent of the reproductive age of population having difficulty in conceiving naturally [1,2], requiring medical intervention to achieve a pregnancy. Female, male or both sexes can have problems causing infertility by factors such as having low quality oocytes, lack of spermatozoa or oocytes, inability of fertilized embryos to grow or implant in the uterus, or issues in spermatozoa's ability to fertilize the oocyte [3]. However, a clear infertility cause is never found out in about 15-30% of patients, which is called 'idiopathic' or 'unexpected' infertility [4].

A considerable example of interdisciplinary methods to cure infertility is laser therapy. This field of medicine is based on biophysics, biochemistry and physiology, leading into new generation of therapeutic techniques with high efficiency [5, 6]. Lasers recently have been employed as a useful tool in the field of assisted reproductive technologies (ART) [3, 7].

Aiming for manipulation or treatment of oocytes and spermatozoa, different kinds of laser sources are used nowadays [8]. One of which is Low-power He-Ne laser that has been employed to improve in vitro production of embryo and treatment of immature oocytes [9]. Infrared diode lasers, is another and the most popular kind of laser with micro- to millisecond pulse time applying usually for microdissection. These kinds of techniques are mostly utilized in the ZP opening in assisted hatching [10, 11]. Pulsed high-intensity laser therapy (HILT) penetrates deeply into the tissue, causing chemical and mechanical changes as well as inducing thermal mechanisms. HILT is effective in treating and reducing endometriosis symptoms and in improving patients' quality of life [12].

However, the full potential of laser therapy can only be achieved through strictly following the standards certified by low level laser therapy (LLLT) and applying appropriate equipment [13]. LLLT is considered as a very efficient approach in physical therapy, utilized in various medicine fields, including andrology, obstetrics and gynaecology, and urology, which is highly recommended as an important part of infertility treatment procedure [14]. In this paper, we reviewed the latest applications of different lasers and their efficacy in the area of infertility treatment.

Causes of male infertility

Male infertility is known as syndrome rooting from a broad range of pathological factors, which are potential to affect body systems including sexual, endocrine, blood, immune and nervous [15, 16]. Statistics demonstrated that around 15 percent of couples suffer from infertility, among which 40-50 percent of cases are diagnosed as male infertility [17].

The success rate of male infertility treatment is considerably high. However, empirical and optimized approach has been reported for idiopathic or genetic male infertility [18].

Multiple reasons can cause male infertility including; failure of testicular, expanding of spermatic veins known as varicocele, dysfunction of endocrine, disturbances in testicular, infection in genital tract, gonadotoxic substances exposure, testicular cancer [19, 20], heat exposure for a long time, smoking, obesity, aging, disturbances in hormones, impotence, retrograde ejaculation [21], pollutants from environment such as radiations, paint, lead and pesticides, tight underwear which enhance the temperature of scrotal environment leading to the sperm production reduction, inadequate vitamin C and zinc in diet, malnutrition, anemia, high exposure to stressful situations, and certain drug taking such as spironolactone, nitrofurantoin and cemitidine [22, 23] (Figure 1).

Causes of female infertility

Female infertility can be rooted from three wide categories including transport, defection in ovulation and implantation [24]. The female infertility are usually diagnosed and attributed to uterine abnormalities, ovulation disorders, peritoneal factors and tubal obstruction. Also, another cause that is assumed to have a minor role is cervical factors, although they are rarely the only cause of the problem [25].

There are several factors that should be taken into account in the initial history including, menstrual intervals, previous use of contraception, frequency and timing of intercourse, infections in pelvic system, number of previous pregnancies, use of certain drugs, substance abuse, exposures to occupational stresses, smoking, alcohol intake, and any previous reproductive organ surgeries [26]. Another significant and basic factor is genetic which can increase the risk of various diseases affecting fertility and reproduction such as uterine fibroids, endometriosis, and age of the person at menarche and menopause [27] (Figure 1).

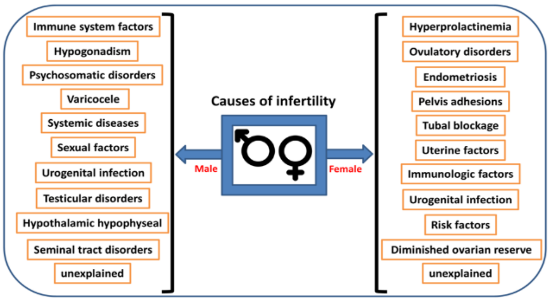

Figure 1 List of causes associated with male and female infertility.

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Laser introduction

Recently, new methods to treat reproduction problems have been proposed based on a novel, effective and more delicate laser systems which are able to generate laser pulses with shorter durations [28]. From the moment lasers have been invented, they are used to study various physiological processes including the determination of spermatozoa motility [5]. Because of its biophysical features, it is almost impossible to use laser light having such parameters effectively in clinical applications. Utilizing a different type of light guide has solved the problem partially by bringing the energy of light to the place needed through cavities, such as illumination of rectum in the prostate gland, and it is possible to use LLLT with pulsed type of the infrared and red (IR) spectrum [13].

The very first kind of solid state laser employed for ART was aimed to grab spermatozoa and it was a neodymium:yttrium-aluminium garnet (Nd:YAG) laser working at 1064 nm wavelength [29]. In order to double the functioning wavelength to 532 nm and ability to drill the zona pellucida, an Nd:YAG laser was reported to be coupled with a potassium titanyl phosphate crystal resulting in well-defined craters in the place when the laser was used tangentially to the oocyte sphere [30]. A considerable concern has been evoked by utilizing the lasers at this very delicate stage of human development, since there are potential risk of embryo development failure, DNA damage, and congenital disorders [31]. Sperm motility and velocity can be increased by irradiation of the low power at spermatozoa using He-Ne laser. This procedure was first reported at the year 1984 [32]. At the cellular level, the mechanism of the low level laser has been attributed to some special components of the cell respiratory chain absorbing near infrared and monochromatic visible radiations. The low-level lase is now considered as an alternative to process various biological applications [33]. Depending on the dosage, condition and wavelength of the irradiated tissue, an anti-inflammatory effect can be inducing by the laser which is potential to accelerate cell proliferation and reduce pain [32]. However, there are some negative outcomes reported regarding motility which may be related to the laser usage features such as power, wavelength, energy density, irradiation time (on cryopreserve sperm), and other conditions of experiment analysis [34, 35].

Types of lasers

Carbon Dioxide Laser

Using the carbon dioxide (CO2) laser was the first step of laser application in skin resurfacing for facial rejuvenation, leading into a new season in photorejuvenation field [36]. To this end, researchers developed short-pulse CO2 lasers to increase control of what type and how much of tissue needs to be removed. However, patients utilizing this method have to pass at least two weeks recovery period. This type of laser emits light the wavelength of 10,600 nm, which is deeply absorbed by skin cells. When the CO2 laser is pulsed at periods less than 1 ms, it vaporizes tissues up to 30 µm per pulse [37] (Figure 2). The relatively new technique of CO2 laser ablation enables high precision of movement and control over tissue penetration depth, which results in smaller mechanical and thermal damage to the ovarian parenchyma [38]. As a result of the procedure, the number of antral follicles does not decrease and the normal ovarian volume can be maintained [39]. This fact is of crucial importance for the procreative plans of the patients as it gives more opportunities of achieving pregnancy in a natural way or with the use of ART. Long-term observations indicate that the chances for a positive therapeutic effect, i.e. a pregnancy, is statistically greater in those patients having the CO2 laser treatment [40].

Helium–neon laser

Like any type of laser, the application of Helium-neon (He-Ne) laser in medicine is based on the light interaction with biological systems. This type of laser works at the wavelength of 632.8 nm and has low output power and photon energy leading in minimum damage on tissues [41]. Since the operation laser elevates temperature no more than 0.5 °C in the irradiated cells, it causes photochemical interactions in the cell environment instead of making thermal effect [42]. In addition, a variety of effects are resulted from the irradiation of He-Ne laser on the function the structure of cell, including adjustment of the cytoskeletal network [43]. The interaction between He-Ne laser and the photoacceptor-cytochrome oxidase of mitochondria can trigger cellular proliferation. This enzyme catalyzes the final biochemical reaction in the mitochondrial respiratory chain in order to transfer electron from cytochrome c to molecular oxygen [44]. Furthermore, this interaction can enhance the electric potential across inner membranes, increase the content on ATP (adenosine triphosphate), and form giant mitochondria. Also, a research has reported the positive effects of low energy lasers working in the red and far red regions of irradiation spectrum on healing of wounds [45] (Figure 2).

Erbium:yttrium-aluminium garnet Laser

The erbium:yttrium-aluminium garnet (Er:YAG) laser was invented in 1992. This type of laser works at 2900 nm wavelength which makes it safe for preventing genetic damages on embryos' structure [46]. However, the Er:YAG laser needs to be operated at direct contact to the embryo, therefore, it may cause some damages and contamination [3]. A few years later, the holmium:yttrium-scandian-gallium garnet (Ho:YSGG) laser was put in the center of attentions, which works at the wavelength of 2100 nm and acts in water in a different way than earlier lasers, facilitating

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its application in this environment without any more necessary micromanipulation [47] (Figure 2).

Potassium Titanyl-Phosphate-Doubled Nd: YAG Laser

Potassium Titanyl phosphate (KTP) laser is considered the most recent advance in technology of laser for transurethral prostatectomy. The frequency of energy in this type of laser is doubled to a wavelength of 532 nm (green-light laser), which selectively can be absorbed by hemoglobin and not totally by water [48]. The Nd:YAG laser was introduced to the reproductive surgeon in 1985 by Lamano [3]. In 1986, the KTP laser became the latest laser to be evaluated and clinically approved for laparoscopic surgery in North America [49]. Nd: YAG laser was the first solid state laser used for ART aiming to trap spermatozoa. It operates at 1064 nm wavelength. Later, Nd:YAG laser was coupled with a potassium Titanyl phosphate crystal in order to enhance the operating wavelength to 532 nm resulting in potential ability to drill the zona pellucida on which distinctive crates were reported when the laser was focused tangentially on the oocyte [3] (Figure 2).

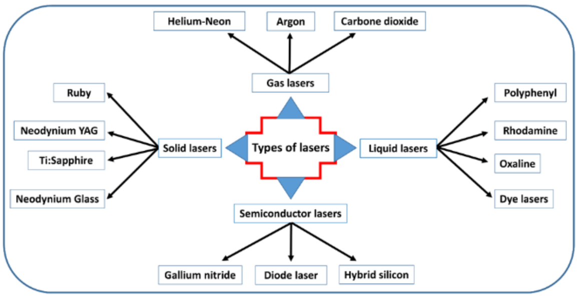

Figure 2 Types of various lasers based on chamber materials.

The application of lasers in male and female diseases

Lasers and endometriosis

One of the most common gynaecological problems and main causes of infertility is endometrial diseases. Endometriosis which is caused by ectopic growth of endometrium-like tissue can affect at least 10% of women at the age of reproduction. The pathogenesis and aetiology of this abnormality are still under research and no effective treatments have been reported till now [50]. As medical therapies and surgery require repeated follow-up and have side effects, it is common for patients to resort to low-cost methods that are both nonmedical and nonaggressive [51]. HILT penetrates deeply into the tissue, causing chemical and mechanical changes as well as inducing thermal mechanisms [52]. HILT fields have physical properties that may be responsible for observed profibrinolytic effects, including mechanical and thermal effects [12]. In a study was demonstrated that deep infiltrating endometriosis is treated by means of radical but fertility-sparing laparoscopic excision with CO2 laser in a multidisciplinary setting [53]. CO2 laser is applied in a multidisciplinary setting for radical treatment but fertility-sparing laparoscopic excision to treat deep infiltrating endometriosis at the Leuven University Fertility Centre (LUFC) is located at the University Hospital Leuven, Belgium, which is known as a tertiary referral center for endometriosis. It has been reported that this method, applied to preserve fertility, is effective in improvement of life quality, sexual satisfaction and pain scores, with a low rate of complication and cumulative recurrence and a high rate of cumulative pregnancy. When CO2 laser is used for endometriosis excision of its 'non-touch' characteristics, it allows the section plane divided diseased and healthy tissue and its precise cutting properties being visualized continuously [54].

Since laser vaporization has been shown to result in a higher rate of cumulative spontaneous pregnancy, clinicians may prefer CO2 laser for endometriosis vaporization rather than monopolar electro-coagulation, to treat women grouped in stage I-II of endometriosis according to ESHRE guidelines [55]. Posadzka et al in 2016 found that a combined method of using classical laparoscopic surgical removal with CO2 laser ablation or electroablation for the treatment of ovarian endometriosis was determined to be effective in the preservation of antral follicle count (AFC) providing a positive evaluation of both techniques in terms of preservation of ovarian reserve [56]. Applications of different lasers on male and female infertility were shown in Table 1.

Table 1. Summery and details of the articles about different lasers application in male and female infertility.

Number	Year	Titles	Main Results
1	2016	Assessment of ovarian reserve in patients with ovarian endometriosis following laparoscopic enucleation of a cyst accompanied by co2 laser ablation or electroablation	Decrease in the detrimental of basal ovarian volume (BOV) after electroablation enucleation and high relapse rate after enucleation after ablation with CO2 laser.
2	2019	Application of femtosecond laser microsurgery in assisted reproductive technologies for preimplantation embryo tagging	Considering femtosecond laser radiation application as an effective way to noninvasively and directly tag embryo which enables identification of embryo for the whole period of preimplantation development.

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3	2014	Effect of diode lasers on human sperm motility	Usage of diode lasers as a useful therapeutic option to cure male factor infertility caused by disordered motility.
4	2018	Effect of pulsed high-intensity laser therapy (HILT) on pain, adhesions, and quality of life in women having endometriosis: a randomized controlled trial	Considering HILT as an effective method to alleviate pain, reduce adhesion, and increase the life quality in women suffering from endometriosis.
5	2016	Helium-neon laser irradiation of cryopreserved ram sperm enhances cytochrome c oxidase activity and ATP levels improving semen quality	A positive correlation between the activity of cytochrome c oxidase (COX) and ATP contents and the motility in irradiated sperm samples. Sperm quality improvement related to the interaction of mitochondria-laser light.
6	2012	Personal overview of the application of LLLT in severely infertile Japanese females	Successful pregnancy induction in over 21% of females being severely infertile, resulting from application of 830 nm LLLT in the technique of proximal priority leading in a substantial number of live births.
7	2009	Outcome after multidisciplinary CO2 laser laparoscopic excision of deep infiltrating colorectal endometriosis	Pain improvement, increase in life quality and sexuality with higher rate of fertility and lower rate of complication and recurrence resulting from Multidisciplinary CO2 laser laparoscopic excision of deep endometriosis with colorectal extension.
8	2013	Safety, efficacy and efficiency of laser-assisted IVF in subfertile mutant mouse strains	Considering Laser-Zona Drilling (LZD) assisted IVF as an efficacious, efficient and safe assisted reproductive technology in order to derive mutant mouse lines having male factor infertility and subfertility which resulted from defects of sperm–zona penetration.
9	2004	Sexual function and satisfaction in men after laser treatment for penile carcinoma	Preserving the penis by laser treatment of localized penile carcinoma and generally providing cosmetic results and satisfactory sexual function.
10	2010	The effects of different laser pulse lengths on the embryo biopsy procedure and embryo development to the blastocyst stage	No influence of Laser pulse length of 0.604 mS, 0.708 mS, and 1.010 mS on the procedure of the embryo biopsy or development of embryo.
11	2015	The effect of low-level laser irradiation on sperm motility, and integrity of the plasma membrane and acrosome in cryopreserved bovine sperm	Beneficial effects of LLLI in the live sperm preservation, in which a 4-joule dose prior to cryopreservation has been shown to be more effective than a 6-joule dose in sperm motility preservation.
12	2011	The effects of laser assisted hatching on pregnancy rates	Significant increase in multiple pregnancy rates of <35 years old patients compared to older patient groups. Considering laser assisted hatching (LAH) beneficial in increasing pregnancy rates after ICSI or IVF in women.
13	2013	The effects of LLLT on the testis in elevating serum testosterone level in rats	Introducing LLLT as a probable alternative treatment modality to conventional methods which are based on testosterone replacement therapy.
14	2012	The effects of low-level laser light exposure on sperm motion characteristics and DNA damage	Involvement of the low-level laser light effect to increase the motility of spermatozoa in the activity of the mitochondrial electron transport chain. No negative effects observed applying the treatment on DNA fragmentation of spermatozoa.
15	2019	Using laser acupuncture and LLLT to treat male infertility by improving semen quality: case report	23% and 24% change reported in the mobility and morphology of sperm. Significant enhancement in sperm volume and sperm count.

Lasers and penile carcinoma

Penis carcinoma is considered as a rare malignancy in western countries, which accounts for about one percent of all cancers diagnosed in the male population [57], the conventional treatment of which is total or partial amputation that almost results in remarkable local control of tumor for low stage disease, but this method also often leads in considerable psychosexual malfunction. The penis can be preserved and local disease can be controlled to the same extent as conventional operations by the application of laser. Thirteen patients were reported to be treated with CO2 laser only but there is a combined usage of Nd:YAG and CO2 laser since 1988 [58].

Lasers and ovarian

Donnez et al (2010) demonstrated that a combined procedure of laser ablative surgery and excisional (cystectomy) without ovarian suture is potentially the best compromise to reserve sparing ovarian [59]. Partial cystectomy or the dissected tissue resection is performed when the hilus is being approached, where the cleavage plane is less visible and the ovarian tissue is more functional. Then, this procedure is followed by using CO2 laser in order to vaporize the remaining small amount (10-20%) of the endometrioma which is close to the hilus. After this operation, the ovary is not closed [60].

Lasers and sperm

These days, male infertility can be effectively treated only with a few therapies, many of which require at least 3 months for success evaluation. All of these therapies usually need a technique for sperm

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preparation attempting to increase the motility of sperm and functional capacity for successful fertilization [61]. There is a mitochondrial sheath tightly coiled in the midpiece of the spermatozoon, which powers the tail movement. ATP production is increased in mitochondria by Low-level laser therapy and 600 – 1000 nm wavelength invokes the light-sensitive cytochrome C oxidase complex located in the electron transport chain of mitochondria to increase the production of ATP. Therefore, the exposure of low-level laser light could enhance the energy level for the motility of sperm in semen samples with poor-quality [62, 63]. The first application of laser in infertility therapy was laser tweezers on spermatozoa where sperms were controlled by a continuous microbeam of laser. Irreversible damages can be made on cell, since lasers operate at the UV and near infrared spectrum. Spermatozoa paralysis and necrosis can be caused, for example, from UV light exposure within 35±20 s and 65±20 s, respectively. However, using lasers in longer wavelengths (above 800 nm) has been shown to be less harmful [64].

A research reported by Guilherme Henrique (2015) demonstrated increased percentage of live sperm cell and sperm motility using LLLT with more positive outcomes, in which he applied wavelength of 660 nm, power of 30 mw and energy of four and six joules for 80-120 s, respectively [65]. Some studies have reported the effectiveness of LLLT and laser acupuncture on improvement of sperm quality. Also, LLLT has been shown to have a better result on sperm motility, in which laser operated for 30s at 905 nm and 50 mw on the genital area, resulting in 85% most promoted in asthenospermic and oligospermic samples and sperm motility [65-68].

Lasers and IVF-ICSI

Through a procedure referred to as 'hatching', the embryo has to move out of the zona pellucida in order to have a successful implementation of that into the uterus. Although lots of researches are working to demonstrate the exact cause of unsuccessful implementation, some involving factors have been reported such as maternal age, decreased endometrial receptivity, and poor embryo and oocyte quality [69-71]. When oocyte and spermatozoa are processed outside of body, followed by planting the fertilized egg in the uterus, it is accomplished through processes termed as in vitro fertilization (IVF), assisted reproductive technologies (ART), and intracytoplasmatic sperm injection (ICSI), all of which have been reported to apply lasers to treat spermatozoa and oocytes [8, 72]. One of the most promising techniques to assist IVF in mice and humans is Laser-zona drilling (LZD). This technique has also been utilized for genetic evaluation of embryos and oocytes by biopsy of the blastomere and polar body. In addition, it has been applied for embryo hatching assistance and injection facilitation of embryonic stem cells into blastocysts or morulae to produce GM mice [10-12, 73]. Tunable Ti: sapphire lasers (650-1080 nm) or Nd:YAG laser (1064 nm or 534 nm) have been used to treat oocytes for ablating zona pellucida or even to make thin holes on its surrounding layer [15]. Diode laser is considered as one of the most effective procedure in permeabilization and immobilization of membrane of human sperm tail before ICSI [74]. It was also reported that spermatozoa samples immobilized by laser need a significant shorter time for identification, injection and aspiration in comparison to the group that was mechanically immobilized. In addition, laser-assisted sperm micromanipulation is well-known as a novel approach in the artificial insemination (Montag, Rink et al. 2000). Application of different lasers with various wavelengths was shown in Table 2.

Table2. The application history of different lasers development in assisted reproductive technology (ART) on different wavelength.

Type of laser	Wavelength (nm)	Application	Reference
Argon Floride (ArF)	193	Puncturing of mouse zona pellucida (ZP), grow to blastocyst	Palanker et al. (1991) [75]
Krypton Floride (KrF)	248	Puncturing of ZP of 2-cell mouse embryos, grow to blastocyst	Blanchet et al. (1992) [76]
Xenon Cloride (XeCl)	308	Puncturing of mouse oocytes prior to improving fertilization with vasectomized mice	El-Danasouri et al. (1993) [77]
Neodymium: yttrium-aluminiumgarnet (Nd:YAG)	532	Puncturing of ZP	Tadir et al. (1991) [29]
He-Ne laser	633	Increase of sperm motility and mitochondrial function in bull	Siqueira et al (2016) [75]
Krypton laser	647	Increase of human sperm motility	Sato et al (1984) [77]
He-Ne laser	660	Increased sperm motility, viability and acrosome integrity in rabbit	Fernandes et al (2015) [76]
Diode laser	830	Improve of sperm progressive motility depending on both laser density and post-exposure time	Yazdi et al (2014) [78]
low-level laser light	905	Increased sperm motility of human without increase in DNA damage	Firestone et al (2012) [63]
Nd:YAG	1064	Trap spermatozoa	Tadir et al. (1989) [78]
Indium gallium arsenide phosphide (InGaAsP)	1480	Non-contact drilling of mouse oocyte ZP	Rink et al. (1994) [53]
Holmium:yttrium scandian gallium	2100	Non-contact drilling of mouse embryo ZP	Neev et al. (1995) [60]

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garnet (Ho:YSGG)			
Erbium-doped yttrium aluminium garnet laser (Er:YAG)	2900	Puncturing of human oocyte ZP prior to IVF	Feichtinger et al. (1992) [61]

Conclusion

Light has always been one of the main basic sources of biological energy since the life inception on earth. Recently, intensive clinical and also basic research is being conducted in the field of laser medicine, aiming to more develop novel therapeutic and diagnostic modalities. Rooted almost equally from men and women, infertility is described as a multifactorial syndrome that covers a wide range of disorders, and a symptom of different types of pathological conditions which affect both the sexual and other systems of body such as endocrine, blood, nervous and immune. Using scientific analysis in this review suggests that laser therapy is able to be applied as much as possible in the complex infertility treatment, since this technique is highly effective and also has no alternatives. Laser technology, for instance, is now used across ART in order to decrease procedure times and also enhance the reproducibility and consistency of traditional techniques of ART such as embryo biopsy, assisted hatching, sperm immobilization and ICSI cryopreservation. This review showed the laser benefits as a powerful technology at the forefront of both therapeutic and diagnostic treatments for female- and male-factor infertility and also general subfertility. However, it should be noted that although lasers are increasingly utilized in ART units, little information relatively is available in the existing literature explaining the potential negative effects of the laser on the developing human embryo, therefore creating the need for further investigations. We hope that, in the future, various types of laser could be used to treat infertility.

Ethical Issue

There was no ethical issue in this systematic review

Conflict of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. Also, this manuscript has not been sent to other journal.

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Author contribution statement

M Y M and J A M wrote the manuscript. H S edited it. All authors have read and agreed to the published version of the manuscript.

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