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Effect of Intrauterine Laser Therapy at the IVF Success Rate on Infertile Patients with a History of IVF Failure: A Pilot Non-Blinded Study

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Abstract

Backgrounds: While there's developing proof aimed toward improving embryo implantation thru a focal point on great development, restrained studies have been performed on enhancing endometrial receptivity. Intrauterine Laser Therapy (LT) can be powerful in selling endometrial cell proliferation, therefore enhancing the achievement of assisted reproductive techniques (ART). The contemporary look at aimed to research the effectiveness of effective intrauterine lasers in growing endometrial thickness and the achievement of being pregnant rate. **Materials and Methods:** In the current clinical randomized trial (RTC) study, the infertile women (20 - 42 years old) referred to the infertility clinic in 2023-2024 who were candidates for IVF treatment with recurrent implantation failure (RIF) history were included. The patients were divided into two main groups: the intervention group; low level laser therapy (LLLT) after hormone administration) (n = 52) and the control group (hormone administration without LT) (n = 52). The IVF success rate and change in endometrial thickness before and after the LT were compared in groups. **Results:** There was a significant difference between groups ($p < 0.05$) regarded to clinical pregnancy rate. Although the endometrial thickness was enhanced in each group after intervention (hormone/laser) ($p < 0.05$), the change in endometrial thickness was not significant between groups. Likewise, in negative or positive clinical pregnancy, the endometrial thickness was enhanced in groups ($p < 0.05$). However, there was no significant difference between groups.

Conclusion: It appears that the incorporation of Intrauterine LT in the realm of infertility could significantly impact as a novel supplementary treatment in improving endometrial receptivity and pregnancy rate.

Keywords

Infertility, IVF, Implementation, Intrauterine Low Level Laser Therapy

1. Introduction

Infertility is described as a pregnancy failure in couples with normal and unprotected sexual sex for three hundred and sixty-five days the anticipated incidence of infertility in ladies of childbearing age is 8 - 12 percent [1]. Assisted reproductive technology (ART) is a well-known method for infertility treatment in which approximately 30% of patients undergoing in vitro fertilization (IVF) successfully achieve pregnancy [2].

Recurrent implantation failure (RIF) is defined as a pregnancy failure after at least two embryo transfers each involving at least two well-developed embryos. Generally, RIF may be attributed to embryo defects or decreased endometrial receptivity [3]. Although increasing evidence is conducted to improve embryo implantation with the most focus on its high-quality development, limited investigations have been conducted on the increasing endometrial receptivity [4]. In this respect, multiple factors such as the endometrial thickness/blood flow and various treatment strategies including hormonal therapy with estradiol, low-dose aspirin, vitamin E, pentoxifylline, tamoxifen, and vaginal sildenafil have the potential to increase the endometrial thickness, and subsequently IVF success [5].

Currently, there has been a significant rise in laser therapy (LT) as a clinical treatment method in tissue healing and organ blood flow enhancement [6] and in many studies, it has been proved that laser therapy enhances the proliferation of various cultured cells [7]. Indeed, it was noted that LT could be effective in increasing uterine blood flow and endometrial cell proliferation, thereby increasing the success of assisted reproductive techniques [8]. For example, in a study conducted by Toshiro *et al*., the potential effect of low-level laser therapy (LLLT) on severe infertility in the Japanese population. The study results reported that the LLLT (830 nm) led to the successful initiation of pregnancy in 21% of severely infertile women along with the painless and side-effect-free [9]. In another study conducted by Youkou Oamaru in 2014, LLL was used T to enhance uterine blood flow in fertility assistance methods, achieving a success rate of 32% [10]. Another study in Denmark in 2017 also showed that using a laser on the abdominal surface increased the success of fertility assistance methods [11]. However, the appropriate mechanisms and medical efficacy of LT are nevertheless now no longer completely comprehended. Accordingly, in addition, investigations are being conducted to reveal the LTs effectiveness on infertility. Taken together, the present day have a look at aimed to research the effective-

ness of local lasers in growing endometrial thickness and the achievement of being pregnant rate.

2. Materials and Methods

2.1. Study Population

The current investigation was a clinical randomized trial (RTC) study. The study population included infertile women (20 - 42 years old) referred to the infertility clinic affiliated with Isfahan University of Medical Sciences in 2023-2024 and were candidates for IVF treatment with recurrent implantation failure (RIF) history. The excluded criteria were: systemic causes of infertility (e.g., rheumatologic diseases), skin lesions at the site of laser treatment, contraindications for hormone therapy (history of cancer or thrombosis), patient dissatisfaction with continuing the study, and cessation of ovulation induction.

The study protocol and all printed information materials received approval from the Human Ethics Committee for the University of Isfahan (IR.ARI.MUI.REC.1402.162).

2.2. Study Intervention

The included patients were divided into two main groups using block randomization and computer software: the intervention group (intrauterine laser therapy after hormone administration) (n = 52) and the control group (hormone administration without laser therapy) (n = 52). The intervention group was undergoing frozen embryo transfer (FET) under laser treatment along with medical treatment as follows: the patients undergo ultrasonography (1st-3rd menstrual cycle) by a specialized individual to assess the endometrial thickness and endometrial blood flow. Subsequently, the estradiol valerate (6 mg/d) was administrated along with the aspirin 80 mg and folic acid 1 mg supplements. Additionally, the laser therapy (6 sessions, three times a week) commenced during the luteal phase (2 days before estradiol implantation). Then, 9th-10th after starting estradiol administration, the patients were reassessed with ultrasonography to evaluate the endometrial blood flow/thickness improvement. Finally, the IVF cycle was accomplished in the 8 - 12 mm endometrial thickness by suppository progesterone 400 mg twice per day was started.

2.3. Laser Therapy Protocol

Laser treatment sessions are performed by a specialist with fixed settings for all patients. The laser beam was irradiated using a cylindrical light diffuser, model RD-ML, Medlight S.A., Switzerland, the projection head was connected to a Webermedical laser fiber. The output power of the laser diode connected to the laser diode was 500 mW, wavelength 880 nm, and the laser was irradiated for 15 minutes. The cylindrical laser light diffuser passes from the vagina and cervix to the uterus. Finally, IVF success rates and changes in endometrial thickness before and after laser treatment were compared in the two main groups.

3. Statistical Analysis

The quantitative and qualitative variables were presented as Mean ± Standard Deviation (SD) and frequency, respectively, and analyzed using IBM SPSS Statistics, version 27.0 (IBM Corp., Armonk, NY, USA). The variables were evaluated using a one-way analysis of variance (ANOVA) (as there are two independent groups. And we want to compare the means of the comparison groups followed by the Tukey post hoc test (for comparing groups with normal distribution) and the chi-square test (for comparing groups with non-normal distribution). A p-value < 0.05 was considered statistically significant.

4. Results

The baseline characteristics are demonstrated in Table 1. In general, 100 infertile women with an average age of 33 years old were included in the current investigation and there was no significant difference between groups. In the current investigation, the major causes of patient infertility were azoospermia, Oligospermia, polycystic ovary syndrome (PCO), ovarian reserve deficiency (ORD), and unknown reason which PCO and ORD had the most impact on infertility that it was noticeable between two groups (P-value = 0.012) (Table 1). It is essential to mention that there was no significant difference between groups in terms of prior pregnancy, abortion, and children number (p-value = 0.374) (Table 1).

Table 1. Baseline characteristics of the study patients.

Variables		Intervention group		Control group		*P-value*
		Number/Mean	Percentage/SD	Number/Mean	Percentage/SD	
Clinical pregnancy	No	28	53.85	37	74	0.034
	Yes	24	46.15	13	26	
Endometrial thickness before treatment		6.77	1.06	6.32	1.05	0.035
Endometrial thickness after treatment		8.8	1.17	8.34	0.63	0.015
Endometrial thickness change		2.04	0.86	2.02	0.96	0.930
Age		33.4	5.55	33.66	5.71	0.819
Infertility cause	Azoospermia	1	1.92	2	4	0.012
	Oligospermia	1	1.92	10	20	
	Polycystic ovary syndrome (PCO)	10	19.23	11	22	
	Ovarian Reserve Deficiency	10	19.23	12	24	
	Unknown reason	30	57.63	15	30	
Prior pregnancy	No	45	86.54	46	92	0.374
	Yes	7	13.46	4	8	

Continued

Children number	**0**	45	86.54	46	92	0.533
	1	2	3.85	2	4	
	2	5	9.62	2	4	
Prior abortion	**0**	49	94.23	48	96	0.512
	1	1	1.92	2	4	
	2	1	1.92	0	0	
	3	1	1.92	0	0	

The clinical pregnancy rate in the two groups is reported in Figure 1. The rate of negative clinical pregnancy was 37 ± 74 and 28 ± 53.85 in the control and case groups, respectively that statistically was reduced ($P < 0.05$). Besides, the positive clinical pregnancy rate was 13 ± 26 and 24 ± 46.15, respectively and there was a significant difference between groups (p-value 0.034) ($P < 0.05$) (Figure 1).

In the control group, the endometrial thickness before and after the hormone administration was 6.32 ± 1.05 and 8.34 ± 0.63, respectively and it was significantly enhanced after hormone therapy (p-value = 0.015) < 0.05) (Figure 2). In addition, laser therapy significantly increased the endometrial thickness (8.8 ± 1.17) in the intervention group (p-value = 0.015) ($P < 0.05$) (Figure 2). However, the change in endometrial thickness was not significant between groups (p-value = 0.930) (Figure 2).

Figure 3 shows the significant relation between the endometrial thickness and clinical pregnancy rate.

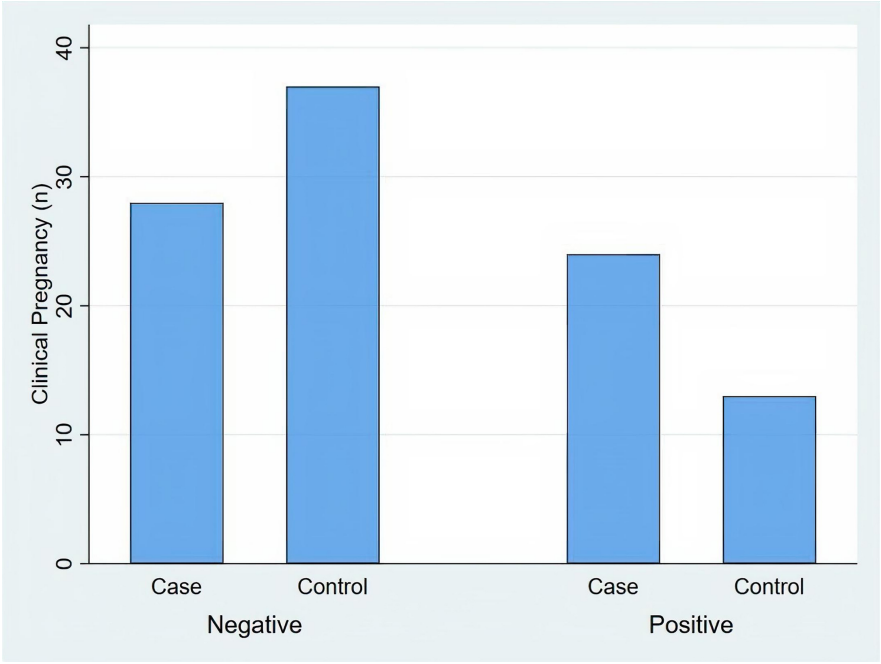

Figure 1. The clinical pregnancy rate in groups.

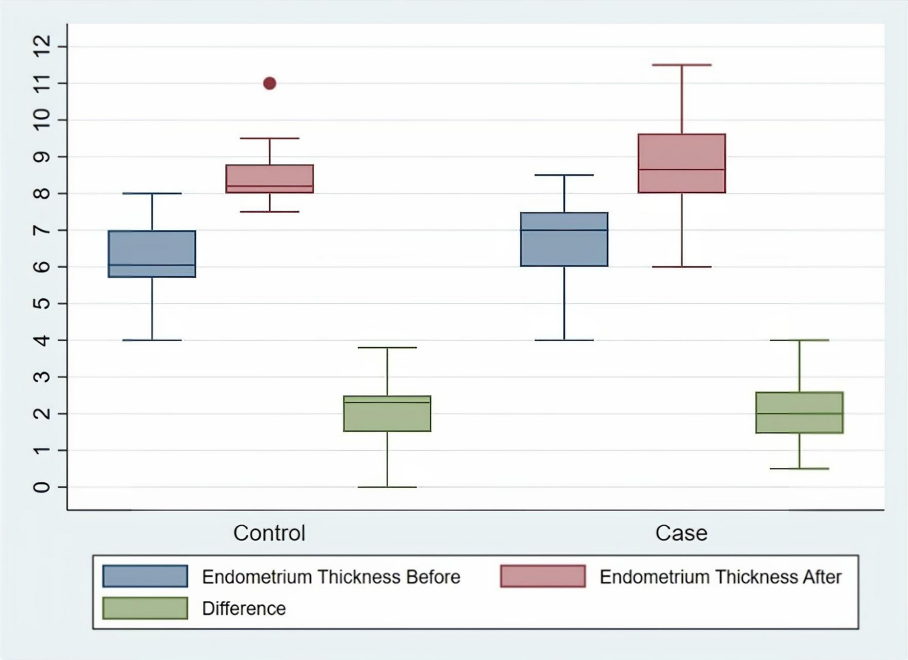

Figure 2. The endometrial thickness rate in groups before and after intervention.

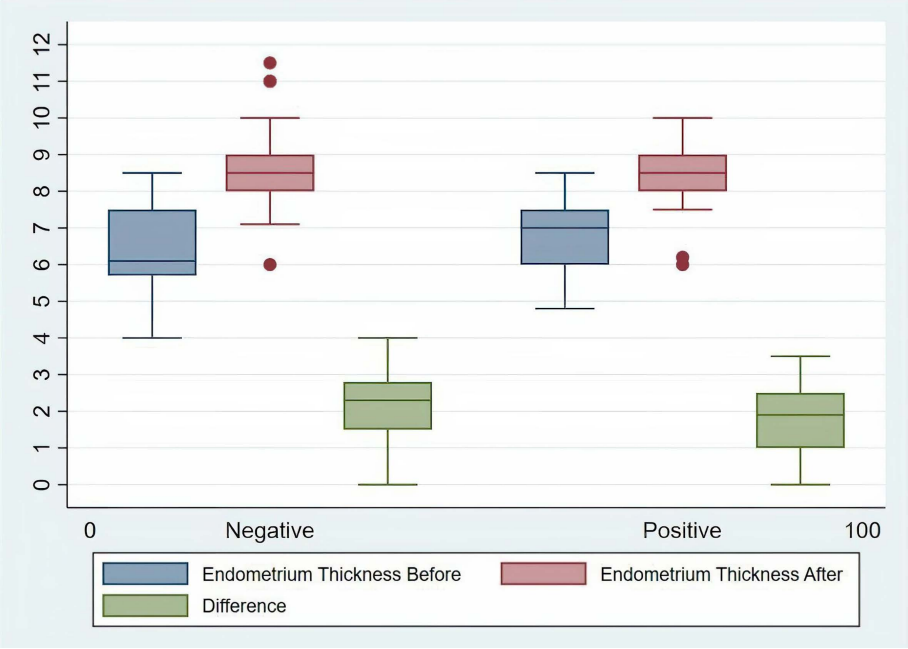

Figure 3. The relation between endometrial thickness and clinical pregnancy rate in groups before and after intervention. This figure shows the significant relation between the endometrial thickness and clinical pregnancy rate. In negative or positive clinical pregnancy, the endometrial thickness was enhanced in groups ($P < 0.05$).

5. Discussion

The present pilot study indicated the LT effect on the IVF success rate in infertile patients with a history of IVF failure. The results demonstrated that polycystic ovary syndrome (PCO) and ovarian reserve deficiency (ORD) had the most

impact on infertility was noticeable between the two groups. In this respect, the study conducted by El-Shamy *et al*., exemplified that laser acupoints could be an effective and safe acupuncture method for treating PCO patients for inducing ovulation [12]. Especially, implementing laser therapy as a new approach enhances ovarian activation by promoting angiogenesis [13].

The main causes of infertility in patients are azoospermia, oligospermia, polycystic ovary syndrome (PCO), ovarian reserve deficiency (ORD) and it is unclear why polycystic ovary syndrome (PCO) and ovarian reserve deficiency (ORD) affect more Infertility was significant between the two groups ($P < 0.05$). It is important to mention that there were no significant differences between the groups in terms of the number of previous pregnancies, number of abortions, and number of children (**Table 1**).

Contemporary investigations are focused on the LT effect on vitrified-warmed embryo switch cycles because of its capacity damage to implantation failure. These studies findings mentioned that the medical being pregnant price becomes statistically more advantageous after LT. Consistent with this result, Ghannadi *et al*., mentioned that laser-assisted hatching (LAH) prompted the medical being pregnant costs for all patients. Additionally, the advantage of LAH in enhancing being pregnant costs after IVF or ICSI in ladies elderly 35 and older become demonstrated [14]. On the other side, the pre-treatment with laser before frozen embryo transfer (FET) could serve as an alternative option for women affected by RIF [15]. In contrast, one of the related studies reported that LAH enhanced the pregnancy rates in FET patients with no enhanced impact on female patients with advanced age or RIF background [16]. Likewise, the failure of embryo implantation in RIF patients may be attributed to the embryo's inability to hatch from its zona pellucida. For example, the clinical implantation rate and live birth rate per embryo transferred (ET) were assessed. The clinical implantation rate with a positive fetal heartbeat per ET was notably higher in patients who received a 4th ET with fresh embryos after modified quarter laser-assisted zona thinning (mQLAZT) compared to patients who had a 4th ET without mQLAZT. Accordingly, mQLAZT may be beneficial in treating RIF patients although further validation is necessary through randomized trials [17].

In two main groups, the endometrial thickness was significantly enhanced after hormone/laser therapy. However, the change in endometrial thickness was not significant between groups. Moreover, the results of the current study revealed that in negative or positive clinical pregnancy, the endometrial thickness was enhanced in groups ($P < 0.05$). However, there was no significant difference between groups. Correspondingly, the intervention with hormone or laser has the potential to increase the endometrial thickness. In line with these findings, the impact of Low-Level Laser Therapy (LLLT) on the proliferation of in vitro cultured endometrial cells was assessed. The study groups compared single (SE) versus multiple exposures (ME) to LLLT and were compared to control groups. Both study groups showed significantly higher numbers of cells compared to the

controls. The surface area of cells at the end of the culture phase was notably larger in the ME group as opposed to the SE group and controls. Properly, the LLLT effectively enhanced the proliferative and functional capacity of cultured endometrial cells [18] [19].

Limitations of this study were small sample size, and the need for better matching between the two groups (case and control).

It is suggested that the comparative therapeutic aspects of low LLLT are assessed in future studies and further studies are required to prove efficacy, treatment protocols such as investigating different wavelengths and doses of therapy, as well as considering the frequency of treatment sessions. Besides, the beneficial effects of low LLLT are regarded as implantation factors.

6. Conclusions

According to the results of this study, it appears that the incorporation of LLLT in the realm of infertility could significantly impact as a novel supplementary treatment in improving endometrial receptivity and pregnancy rate. However, further clinical investigations are needed to prove the potential therapeutic aspects of LLLT in infertility issues. With new technologies such as the capabilities of interstitial and intrauterine lasers, more research could be performed based on these advanced methods.

In our study, it was suggested that laser therapy could be beneficial in treating infertility in assisted reproductive techniques. However, due to limitations such as a small sample size, and the need for greater synchronization between the two groups (case and control), further studies are required to prove efficacy. This includes investigating different wavelengths and doses of therapy, as well as considering the frequency of treatment sessions.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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