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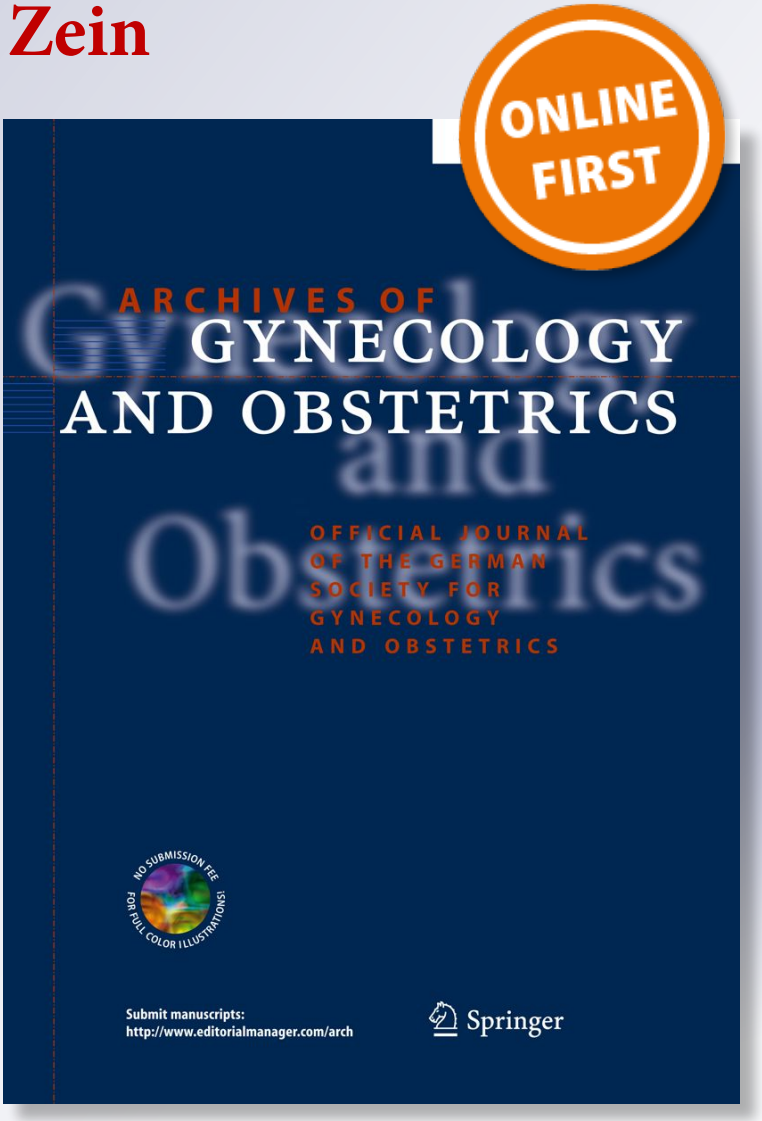

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GYNECOLOGIC ENDOCRINOLOGY AND REPRODUCTIVE MEDICINE

Effect of laser-assisted zona thinning, during assisted reproduction, on pregnancy outcome in women with endometriosis: randomized controlled trial

Adel Mohamed Nada[1] · Amr El-Noury[2] · Hesham Al-Inany[1] · Mamdouh Bibars[3] · Tamer Taha[3] · Sameh Salama[3] · Fatma Hassan[3] · Eman Zein[4]

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Abstract

Objective To compare the ICSI-ET outcomes in patients with endometriosis with or without laser-assisted zona pellucida thinning.

Design Randomized controlled trial.

Setting The study was conducted in the Obstetrics & Gynecology Department, Cairo University hospital, and two private IVF centers in Cairo & Beni-Suif from July 2015 to January 2017 upon infertile and known endometriosis patients who planned to do ICSI-ET.

Interventions Before randomization, all patients received the same ovarian stimulation preparation, oocyte retrieval procedures, and the same intracytoplasmic sperm injection procedures. After randomization, laser-assisted hatching was performed only for embryos of 158 patients, while the other group ($n = 150$) no laser-assisted hatching was made. The verification of pregnancy was achieved by the serum hCG concentration 14 days after the embryo transfer, and the clinical pregnancy was confirmed 2 weeks later by the presence of gestational sac with pulsating fetal pole on vaginal ultrasonography.

Measurements The main outcome measures were the clinical pregnancy rate and the clinical implantation rate.

Main results Both groups were comparable with regard their baseline characteristics, baseline hormonal profile, the ovarian stimulation characteristics, and the ovulation characteristics. The mean number of embryos developed per patient and the mean transferred number of embryos per patient were comparable between groups (p value > 0.05). The implantation rate was significantly higher (p value 0.002) in the study group than the control group with an odds ratio of 1.86 (CI 95% 1.24–2.80) and NNT 13.81 (CI 95% 8.35–39.94). The clinical pregnancy rate, was significantly (p value 0.022) higher in the study group than in the control group with an odds ratio of 1.79 (CI 95% 1.05–3.06) and NNT 9.57 (CI 95% 5.03–98.99).

Conclusion That laser-assisted hatching by thinning of the zona pellucida may be a suitable method to improve the ICSI-ET outcomes, in term of the implantation and the pregnancy rates, in cases of endometriosis.

Clinical trial registration Pan African Clinical Trials Registry (PACTR), http://www.pactr.org/ATMWeb/appmanager/atm/atmregistry?dar=true&tNo=PACTR201502001022393, PACTR201602001467322.

Keywords Laser-assisted zona pellucida thinning · Endometriosis · ICSI-ET outcomes

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Introduction

Endometriosis is the presence of endometrial tissue outside the uterine cavity, and it has a prevalence rate of 10–15% of women in the reproductive age [1]. Approximately, 30–50% of them presents with infertility. Also, endometriosis accounts for 25–50% of infertile women [1, 2].

Despite that the exact mechanism of infertility in patients with endometriosis is not well-understood up till now, there are several proposed mechanisms such as a distorted

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anatomy of the pelvis, impaired function of the ovary, inadequate endometrial receptivity, and reduced quality of the oocytes/embryos [3, 4].

The most efficient management of infertility in those cases is the assisted reproductive technology [5]. However, the impact of endometriosis on the outcomes of Intra-Cytoplasmic Sperm Injection procedures-Embryo Transfer (ICSI-ET) has not been well understood nor has consensus up till now. For example, some studies suggested that the inferior results of ICSI-ET in those type of patients may be due to a lower number of oocytes retrieved; oocytes/embryos of affected quality; or impaired endometrial receptivity [6, 7]. On the contrary, several studies showed that the ICSI-ET outcomes are comparable to patients with infertility due to tubal factors [5].

There are several options offered to improve the ICSI-ET outcomes in those cases. Many researchers have studied the hatching process and the ways to improve it. This technique has been used for helping the embryo exit of zona pellucida and its implantation. First, they used mechanical and biochemical methods [8]. Recently, the utilization of laser for assisting hatching has begun [8]. Initially, it was used to create a single full-thickness hole in the zona pellucida (drilling) before embryo transfer to the uterus. This method is called the assisted hatching by drilling [8, 9]. Another technique for the assisted hatching which was studied and demonstrated a significant increase in hatching in vitro [10] as well as a higher clinical pregnancy rate [11], is the utilization of the laser to thin an extensive area of the zona pellucida (zona thinning). Padula et al. [12] compared the two methods: the zona drilling and the zona thinning. The authors did not find any statistically significant advantages of drilling, and they recommended the implementation of the zona thinning [12]. With a wide variation in the methodology, laser zona thinning became a well-known technique [8].

Up till now, to the best of our knowledge, there was only one research that studied the impact of laser-assisted hatching on ICSI-ET outcomes in patients with endometriosis. This research was a randomized study but with a relatively small sample size (90 cases) [13].

Thus, the rationale intended for this parallel randomized controlled study was to compare the ICSI-ET outcomes in patients with endometriosis with or without laser-assisted hatching.

Materials and methods

The study was conducted in Obstetrics & Gynecology Department, Cairo University Hospital unit, and two private IVF centers in Cairo and Beni Suif during the period from July 2015 to January 2017. This study conformed to the principles of the Declaration of Helsinki and following the Medical Research Involving Human Subjects Act (WMO). It was approved by the medical ethical review committee of Cairo University. The purpose of this study was clearly explained in the Arabic language to all subjects before their enrollment to the study, and an informed consent form was signed by and obtained from all of those enrolled.

We recruited all infertile women with endometriosis in the reproductive period, age from 18 to 39 who planned to undergo assisted reproduction. All patients were scheduled for a full history, physical examination, ultrasound, hormonal profile, and diagnostic laparoscopy to confirm the presence of endometriosis. The diagnosis of endometriosis was made according to the American Society for Reproductive Medicine criteria (1997) [14].

Exclusion criteria included: age more than 39 years, very poor male parameters such as abnormal forms of sperms more than 96% and poor ovarian responders.

Randomization and blinding

For allocation of the participants, a computer-generated list of random numbers was used. Block randomization with a block size of 4 was used with 1:1 ratio of the study group (laser-assisted hatching) and the control group (no laser-assisted hatching).

The allocation sequence of subjects was concealed from the researcher assessing the implantation and the pregnancy; hence, he did not know the relation between the patients' numbers and the allocation sequence.

Procedures

Before randomization, all patients have received long-acting GnRH agonist (decapeptyl, Ferring, Switzerland) 3.75 mg intramuscular injection per month for 2 months, and were scheduled for controlled ovarian hyperstimulation by long GnRH agonist (decapeptyl, Ferring, Switzerland) 0.1 mg subcutaneous injection per day starting from the midluteal phase.

The complete pituitary suppression confirmed by serum E2 level < 30 pg/mL and serum LH level < 5mIU/mL, and then gonadotropin therapy started from day 2 to day of follicular maturation confirmed by the presence of three mature follicles or more with size more than 16 mm and one of them more than 17 mm. At this time, 10,000 IU of hCG was administrated then ovum pick up was done after 36 h.

The retrieved oocytes were kept in a culture medium (Global® for fertilization, LifeGlobal, CT, USA) using a protein supplement 10% (LGPS, LifeGlobal, Connecticut-USA). Then, it was covered by paraffin oil (Paraffin oil P.G., LifeGlobal, Connecticut, USA) for a period of 2–3 h before the removal of the cumulus cells. The surrounding cumulus cells were removed after exposure to an

HEPES-buffered medium with hyaluronidase (80 IU/mL, LifeGlobal, Connecticut, USA). The remaining cumulus cells were removed mechanically by gently pipetting with a hand-drawn Pasteur pipette (Humagen Fertility Diagnostics, Charlottesville, USA).

Oocyte morphology was estimated by an inverted Nikon Diaphot microscope (Eclipse TE 300; Nikon®, Tokyo, Japan) with a Hoffmann modulation contrast system under 400× magnification this done just before sperm injection (4 h after retrieval). Oocyte morphology was assessed for any intracytoplasmic dysmorphisms. Oocytes were rinsed and preserved in 3 ml of fertilization medium (G-IVF PLUS, Vitrolife, Göteborg, Sweden) until the preparation of the sperm. The gradient method was used for the preparation of the sperm. Hence, the sperms were suspended in the same fertilization medium in the incubator until employment of ICSI. Our study included patients who had enough sperms for ICSI at the normal morphology and motility according to the WHO classification. ICSI was made for all patients.

Intracytoplasmic sperm injection was performed in a microinjection dish prepared with 4-µL droplets of buffered medium (Global® w/HEPES, LifeGlobal, Connecticut, USA) and covered with paraffin oil on the heated stage of an inverted microscope at 37.0 ± 0.5 °C. Approximately 16 h after ICSI, fertilization was confirmed by the presence of two pronuclei and extrusion of the second polar body. Embryos were maintained in a 50-µL drop of culture medium (Global®, LifeGlobal, CT, USA) with 10% protein supplement and covered with paraffin oil in a humidified atmosphere under 6% CO_2 at 37 °C for about 3 days.

After fertilization, zygotes were cultured in microdroplets of cleavage medium (G1 PLUS, Vitrolife, Göteborg, Sweden) about 20 µL at 37 °C under 6% CO_2. Routine embryo evaluation was carried out by using the Scott's scoring system after 16–18 h following ICSI. The parameters of the assessment of embryos by the stereomicroscopy included the number and quality of the blastomeres, the percent of fragmentation, a variation in blastomere symmetry, the presence of multinucleation, and defects in the zona pellucida and cytoplasm. High-quality cleavage-stage embryos were defined as those with all of the following characteristics: 8–10 cells on day three, < 15% fragmentation, the absence of multinucleation, symmetric blastomeres, the absence of zona pellucida dysmorphism, and the absence of perivitelline space granularity and colorless cytoplasm with moderate granulation and no inclusions. Embryos lacking any of these characteristics were considered to be of low-quality, the best-quality, or good-quality fresh grade 1 embryos were selected for intrauterine transfer maximum 2–3 embryos in each embryo transfer cycle. After the selection of embryos to be transferred, we performed the randomization between both the study group and the control group.

After randomization, laser-assisted hatching was performed for embryos of 150 patients with endometriosis only (the study group) just before the embryo transfer. Zona pellucida thickness of an embryo was estimated by calculating the mean of four measurements of zona pellucida thickness which performed on that embryo. It was carried out in a standard manner. Briefly, a 1.48-µm infrared solid-state diode laser (Saturn 3, England) in a computer-controlled non-contact mode was used. After the positioning of the embryo, it was focused at the equatorial level of the zona pellucida. The used pulse length was 2.8 ms. The zona pellucida of each embryo was exposed to the laser three times, each of them at one point and continued until an average of 25–30% was dissolved using three adjacent pulses.

Embryos of all 308 patients were transferred on day 3 after oocyte retrieval. Injections with 100 mg progesterone intramuscularly were administrated as luteal phase support from the day of oocyte retrieval to the time of doing the pregnancy test. The verification of pregnancy was achieved by the serum hCG concentration 14 days after the embryo transfer. Thus, the chemical pregnancy rate was reported. Then, the clinical pregnancy was confirmed by the presence of gestational sac—with pulsating fetal pole at 6 weeks gestation—on vaginal ultrasonography.

Outcome measures

The primary outcome measure was the clinical pregnancy rate (CPR) per initiated cycle. The clinical pregnancy was defined as a serum hCG level > 20 IU/L and confirmed by observation of gestational sac with pulsating fetal pole on transvaginal ultrasound scan 4 weeks after transfer or 6 weeks post-menstrual.

The secondary outcome measures: the live birth rate and the implantation rate per embryo transferred defined as the number of gestational sacs present on ultrasound scan 4 weeks after transfer divided by the number of embryos transferred [3].

Statistical analysis and sample size justification

A sample size calculation was done to calculate the number of subjects needed in each group. Reference to Nadir Çray et al. [13] the pregnancy rate in the intact Zona group was 40%. We assumed that the pregnancy rate in the laser-assisted hatching group would be 57%, with a significance level of 0.05 and 80% power, at least 268 patients (134 patients per group). A total sample size of 350 was required to consider any drop outs.

All statistical analyses were made by the intention to treat analysis method. All statistical tests were made using a significance level of 95%. A p value < 0.05 was considered statistically significant. SPSS software (Statistical Package

for the Social Sciences, version 20.0, SPSS Inc, Chicago, IL, USA) was used for the statistical analyses. Data were presented as (mean ± SD) or median (range) for continuous variables and as frequency and percent for categorical variables. Comparisons between groups were made using Chi-square test for categorical variable and the independent *t* test for the continuous variables.

Results

All subjects (350) who came to the center and were eligible for ICSI-ET due to endometriosis were asked to participate in the study. Six subjects refused to participate, and 18 subjects were excluded before randomization because they did not meet the inclusion criteria, leaving 326 participants for randomization with 163 assigned to each group. Eighteen subjects were excluded after randomization due to cycle cancelation. The dispositions of these subjects are shown in Fig. 1.

Baseline characteristics

Both the laser-assisted hatching group and the control group were comparable with regard their baseline characteristics and baseline hormonal profile. There was no statistically significant difference ($p > 0.05$) between the two groups regarding the age, BMI, the duration of infertility, as well as its type, as shown in Table 1. More than 75% of subjects in both groups were overweight or obese (BMI > 25). Also, the two groups were comparable ($p > 0.05$) regarding the LH level, FSH level, the estradiol (E2) level, as shown in Table 1.

Ovarian induction, ICSI parameters, and oocytes' characteristics

Both the laser-assisted hatching group and the control group were comparable with regard the stimulation characteristics in term of days of stimulation and endometrial thickness at the transfer time (p value > 0.05), as shown in Table 2. Also, in both groups, the ovulation characteristics in term of AFC, the goodness of the response,

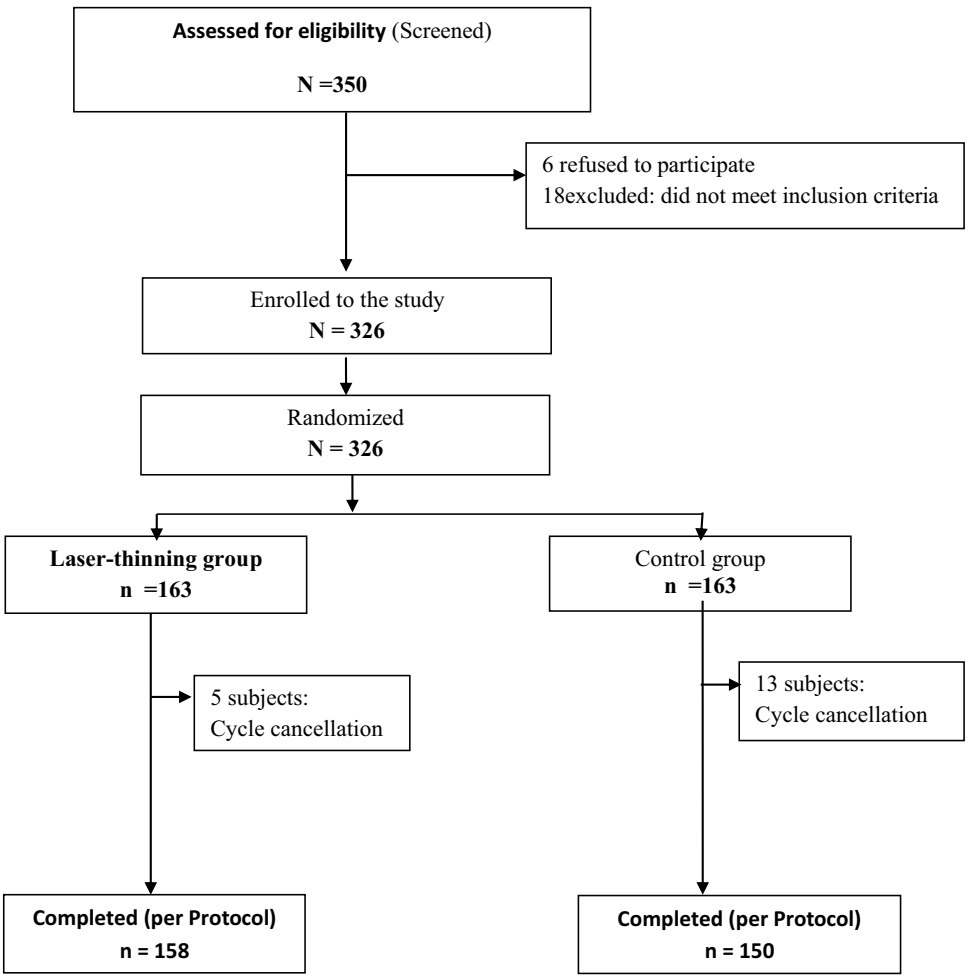

Fig. 1 CONSORT diagram

Table 1 Baseline characteristics

	The laser-assisted hatching group, $N = 158$	The control group, $N = 150$	p value
Age in years, mean (SD)	31.27 (4.06)	32.64 (3.55)	0.346
BMI (kg/m^2), mean (SD)	27.03 (2.64)	27.26 (2.38)	0.212
Type of infertility			
Primary	105 (66.46%)	103 (68.67%)	0.679
Secondary	53 (33.54%)	47 (31.33%)	
Duration of infertility in years, mean (SD)	4.87 (1.31)	4.63 (1.69)	0.246
Basal hormonal profile on day 2 at initial visit			
LH (mIU/mL), mean (SD)	5.11 (1.31)	4.81 (1.11)	0.098
FSH (mIU/mL), mean (SD)	5.36 (1.61)	5.99 (1.06)	0.285
E2 (pg/mL), mean (SD)	41.90 (9.93)	42.97 (8.16)	0.270

Table 2 Ovarian induction, ICSI parameters, and zona pellucida thinning

	The laser-assisted hatching group	The control group	p value
Stimulation characteristics			
Stimulation days, mean (SD)	11.56 (1.95)	11.93 (1.92)	0.284
Endometrial thickness at transfer mm, mean (SD)	10.47 (1.88)	11.01 (1.58)	0.170
Ovulation characteristics			
AFC, mean (SD)	8.58 (1.47)	9.39 (1.77)	0.135
Oocyte retrieved number, mean (SD)	9.94 (2.47)	10.69 (2.30)	0.594
M1, mean (SD)	3.18 (1.55)	3.65 (1.68)	0.147
M2, mean (SD)	4.99 (1.31)	5.13 (1.33)	0.689
GV\EZ, mean (SD)	0.97 (0.76)	1.07 (0.81)	0.124
Fertilization characteristics			
Number of embryos, mean (SD)	4.63 (1.38)	5.17 (1.20)	0.698
G1 embryo grade, mean (SD)	2.87 (0.91)	3.23 (0.86)	0.774
Transfer number, mean (SD)	2.44 (0.50)	2.87 (0.33)	0.217

the oocyte retrieval and the oocyte retrieved number; as shown in Table 2.

Fertilization characteristics were comparable between both groups ($p > 0.05$). The mean number of embryos developed per patient was 4.63 ± 1.38 in the laser-assisted hatching group and 5.17 ± 1.20 in the control group (p value 0.698).

The mean number of the good embryo grade (G1) was 2.87 ± 1.38 in the laser-assisted hatching group and 3.23 ± 0.86 in the control group (p value 0.774). The mean number of embryos transferred per patient was 2.44 ± 0.50 in the laser-assisted hatching group and 2.87 ± 0.33 in the control group (p value 0.217). We have no single embryo transfer (SET) in our study. Details of number of duplet embryo transfer (DET) and triplet embryo transfer (TET) in both groups are shown in Table 3.

Implantation rate

The implantation rate was significantly higher (p value 0.002) in the study group than the control group. In the study group, 67 fetuses from 385 transferred embryos versus 44 fetuses from 431 transferred embryos in the control group. The implantation rate elevation was 7.24 (CI 95% 2.50–11.98) with an odds ratio of 1.86 (CI 95% 1.24–2.80) and NNT 13.81 (CI 95% 8.35–39.94). Details of number of implanted embryos are shown in Table 3.

Pregnancy outcomes and live birth rate

The clinical pregnancy rate, as confirmed by US, was significantly (p value 0.022) higher in the study group than in the control group. It was 29.11% in the study group and 18.67% in the control group. The pregnancy rate elevation

Table 3 Number of embryos transferred, implanted, and number of fetuses

	The laser-assisted hatching group	The control group	*p* value
Number of embryos transferred	385	431	
SET	0	0	< 0.001
DET	89	19	
TET	69	131	
Number of implanted embryos	67	44	
One embryo	30	16	0.780
Two embryos	11	8	
Three embryos	5	4	
Number of fetuses	46	28	
Singleton	30 (65%)	16 (57%)	0.780
Twins	11 (24%)	8 (29%)	
Triplets	5 (11%)	4 (14%)	

was 10.45 (CI 95% 1.01–19.88%) with an odds ratio of 1.79 (CI 95% 1.05–3.06) and NNT 9.57 (CI 95% 5.03–98.99), as shown in Table 4.

The live birth rate was significantly (*p* value 0.043) higher in the study group than in the control group. It was 25.32% in the study group and 16.67% in the control group. The rate elevation was 8.65 (CI 95% 0.38–17.68%) with an odds ratio of 1.69 (CI 95% 0.97–2.97) and NNT 11.56 (CI 95% 5.66–263.16), as shown in Table 4.

Numbers of the resulted fetuses were comparable between both groups (*p* value 0.780). In our study we have twins in 11 (24%) cases of the study groups versus 8 (29%) in the control group. Moreover, we have triplets in five (11%) cases of the study groups versus four (14%) in the control group.

Table 4 Implantation rate and pregnancy rate

	The laser-assisted hatching group	The control group	*p* value
Total number of embryo transferred	385	431	
Implantations rate, *n* (%)	67 (17.40%)	44 (10.16%)	*0.002*
Rate in the study group (CI 95%)	17.40		
Rate in the control group (CI 95%)	10.16		
Rate elevation	7.24 (2.50–11.98)		
Odds ratio	1.86 (1.24–2.80)		
Number needed to treat	13.81 (8.35–39.94)		
	N = 158	N = 150	
Pregnancy rate, *n* (%)	46 (29.11)	28 (18.67)	*0.022*
Rate in the study group (CI 95%)	29.11		
Rate in the control group (CI 95%)	18.67		
Rate elevation (CI 95%)	10.45 (1.01–19.88)		
Odds ratio (CI 95%)	1.79 (1.05–3.06)		
Number needed to treat (CI 95%)	9.57 (5.03–98.99)		
	N = 158	N = 150	
Live birth rate, *n* (%)	40 (25.32)	25 (16.67)	*0.043*
Rate in the study group (CI 95%)	25.32		
Rate in the control group (CI 95%)	16.67		
Rate elevation (CI 95%)	8.65 (0.38–17.68)		
Odds ratio (CI 95%)	1.69 (0.97–2.97)		
Number needed to treat (CI 95%)	11.56 (5.66–263.16)		

p values are shown in italics

Discussion

Researches on the ART outcomes in infertility associated with endometriosis have described conflicting results in the advanced-stage endometriosis, with some reported worse outcomes and others described comparable outcomes. The poor-outcome-reported studies suggest that patients with infertility due to endometriosis who were offered the ART show poor ovarian response, lower fertilization rates, decreased endometrial receptivity, and reduced implantation rates. It has also been suggested that the quality of oocyte and embryo may be compromised in patients with endometriosis-associated infertility [15].

Moreover, women with endometriosis undergoing ART have a significantly lower oocyte yield and lower fertilization rates in comparison with tubal factor infertility [14]. However, another study described that in addition to the lower fertilization rate and similar implantation rates between subjects with and without endometriosis, infertile women with endometriosis have comparable pregnancy rates and live birth rates to women with tubal factor infertility, even after adjusting for confounding factors [16].

A meta-analysis by Barnhart et al. [17] concluded that patients with endometriosis-associated infertility undergoing IVF respond with significantly lower levels of all markers of the reproductive process, resulting in a pregnancy rate that is almost half of that of women with other indications for IVF. The authors suggested that endometriosis affects not only the receptivity of the endometrium but also the development of the oocyte and the embryo [17].

Embryo implantation depends on three factors: proper embryo development, a receptive endometrium, and appropriate interaction between them [18].

Hatching, the breaching of the embryo from the zona pellucida, is essential for implantation. Thus, many methods have been proposed to assist the process. Some studies showed higher implantation and pregnancy rates when assisted hatching was applied to transfer embryos, while others reported no difference in the outcome. Nevertheless, one study recommended the routine application of assisted hatching to increase the implantation potential of embryos [13].

Laser-assisted hatching by zona pellucida microdissection can be done with high precision and repeatability with no negative impact on in vitro embryo development [19]. The technique is easy to perform and very effective concerning the overall time requirement and can be made in a sterile environment without any additional micromanipulations by using the infrared 1.48-µm diode laser. The safety of the 1.48-µm diode laser beam has been evaluated in mouse and human oocytes and zygotes [20].

In our RCT study, we used the laser-assisted hatching as a method to improve the ICSI-ET outcomes in patients with endometriosis and compared it to no hatching. The results of this study showed that laser-assisted hatching might be an effective method to improve the ICSI-ET outcomes in those patients.

The results of our study showed that laser significantly succeeded in reducing the zona pellucida in the study group. The implantation rate was significantly higher in the study group than the control group. In addition, the clinical pregnancy rate, as confirmed by US, was significantly greater in the study group than in the control group. Moreover, the live birth rate is significantly higher in the study group than the control group. The results of our study show that the implantation capacity of embryos in endometriosis may be improved by the manipulation of the zona pellucida. This indicates that breaching of the embryo may be a problem in those types of patients.

Contrary to our study, the results of Nadir Çray et al. [13] concluded that the laser-assisted hatching does not improve the outcomes of the assisted reproduction in women with endometriosis in term of the implantation rate and the pregnancy rate. However, it should be noted that the statistical power of his study is not enough due to the small number of the sample size and the small number of cycles. Hence, the results are not reliable enough. Moreover, this study excluded cases with zona pellucida thickness more than 15 µm which is not the case in our study [13].

One interesting finding of our study was that we have high multiple pregnancies. That is because the routine practice in Egypt is to transfer three embryos. Patients accept that, as multiple pregnancies are better than failure. The procedure is expensive and not covered by medical insurance, so, most of couples accept multiple pregnancies more than failure of pregnancy. Moreover, sometimes, patients ask to transfer only two embryos, and sometimes, we transfer only two because we have only two grade one embryos. In our study, more embryos transferred in the control group and we have more pregnancy in the study group and this support the results of our study.

The advantage of this study is that it was a well-designed randomized controlled powered trial with enough sample size. However, one limitation of the study is that the stages of endometriosis were not reported which may affect the results of the study.

Conclusions

Finally, we conclude that laser-assisted hatching by thinning of the zona pellucida may be a suitable method to improve the ICSI-ET outcomes, in term of the implantation and the pregnancy rates, in cases of endometriosis. Thus,

we recommend using this technique for patients with endometriosis. We recommend a larger study to determine the predictors of the success of the laser-assisted hatching.

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Author contributions AE, HA, AMN, MAB, TT, SS, FH, and EZ contributed to conception of the idea and design. AMN, MAB, FH, and EZ administered the study and collected the data. Validation was performed by AE, HA, MAB, TT, SS, and EZ. Analysis was carried out by AMN, FH, and EZ. AE, HA, AMN, MAB, and FH drafted the manuscript. Revision of the final manuscript was carried out by AE, HA, AMN, MAB, TT, SS, FH, and EZ.

Compliance with ethical standards

Conflict of interest Adel M. Nada declares that he has no conflict of interest. Amr El-Noury declares that he has no conflict of interest. Hesham Al-Inany declares that he has no conflict of interest. Mamdouh Bibars declares that he has no conflict of interest. Tamer Taha declares that he has no conflict of interest. Sameh Salama declares that he has no conflict of interest. Fatma Hassan declares that she has no conflict of interest. Eman Zein declares that she has no conflict of interest.

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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