

Short Communication

Simultaneous laparoscopy for endometriotic women undergoing *in vitro* fertilization

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Abstract

Objective: The aim of this study was to investigate simultaneous laparoscopy in endometriotic women with infertility undergoing *in vitro* fertilization (IVF).

Materials and Methods: Forty-seven infertile patients with endometriosis were enrolled in this retrospective study and underwent IVF cycles in a university affiliated hospital.

Results: The chemical pregnancy, clinical pregnancy and live birth rates were statistically significantly different between patients with minimal or mild stage endometriosis and patients with moderate or severe stage endometriosis, who received simultaneous laparoscopy and modified IVF with a GnRH antagonist protocol. A higher live birth rate was achieved in IVF patients with minimal or mild stage endometriosis combined with laparoscopic treatment, than in patients who received traditional IVF with prior laparoscopic surgery for endometrioma.

Conclusion: Simultaneous laparoscopy combined with a modified IVF (GnRH antagonist) protocol may benefit patients with minimal and mild endometriosis. Traditional GnRH agonist IVF cycles may improve the fecundity rates in women with moderate and severe endometriosis after laparoscopic treatment.

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Introduction

Endometriosis affects approximately 10–20% of women of reproductive age, while among infertile women, the prevalence is estimated to range between 30% and 50% [1]. With the recent advance of ultrasonography [2,3], ultrasound examination is useful in the differential diagnosis and in planning medical or surgical intervention for endometriosis. Medical treatment with gonadotropin-releasing hormone (GnRH) agonists prior to *in vitro* fertilization (IVF) cycles is associated with an increase in pregnancy rate, but clinical

therapy alone is considered insufficient for treating endometriosis-associated infertility [4]. The surgical purposes for patients suffering from endometriosis are to confirm the pathohistology and severity of the involved area, and to relieve the symptoms, such as dysmenorrhea and pelvic pain [5]. Besides, we need to exclude the possibility of malignancy in cases with endometrioma > 3 cm [3,6]. Laparoscopy remains the gold standard for treatment of endometriosis, as it can coagulate all visible endometriotic lesions and excise associated pelvic or visceral adhesion by using the see and treat method [7]. It serves as a less invasive and cost effective approach, when compared to laparotomy, for endometriosis surgery. Laparoscopic surgery also diminishes the cost, morbidity and the recurrence rate of postoperative pelvic adhesions.

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The old aphorism ‘when in doubt, cut it out’ has been replaced with a more evidence-based approach, that tries to balance carefully the advantages as well as the complications of cyst removal prior to an IVF cycle [1]. The benefits of surgical therapy for infertility associated with endometriosis have been well documented [8–11]. Laparoscopic surgery before IVF cycles, not only offers the advantage of making a decision about the treatment course, but also for establishing a good pelvic environment to enhance pregnancy during IVF cycles in infertility treatment in patients with ovarian endometriomas [12,13]. Recently, with the advent of IVF, the number of patients undergoing diagnostic laparoscopic evaluation as part of the initial workup has decreased. Owing to the high rates of recurrence (approximately 50% after 5 years of therapy cessation) [14–17], we are frequently presented with a dilemma between performing IVF, or adopting a surgical approach, as the first choice to achieve better results when treating an infertile couple. Most published data is in favor of the hypothesis that laparoscopic surgical removal of ovarian endometrioma prior to IVF does not offer any additional benefit in terms of fertility outcomes [18,19], but may decrease the ovarian response to gonadotropins. The presence of endometriomas does not obviously affect the ovarian response to hyperstimulation in endometriotic women during IVF treatment. In addition, the pregnancy rate, following combined treatment with laparoscopy and subsequent IVF, in women with endometriosis associated infertility, is higher than that following no treatment, surgery or IVF alone [20]. The aim of this study is to display the therapeutic effect of simultaneous laparoscopic surgery for endometriosis-associated infertility during IVF treatment.

Materials and methods

This study was approved by the Institutional Review Board of National Cheng Kung University Hospital. Forty-seven infertile patients, who received laparoscopic surgery for endometriosis and/or endometrioma, were enrolled retrospectively through our IVF database system from January 2004 through January 2008. The inclusion criteria were: (1) symptoms of endometriosis and/or endometrioma; (2) history of laparoscopic surgery for endometriosis and/or endometrioma; and (3) histologically confirmed diagnosis of endometriosis and/or endometrioma. Patients who received exploratory laparotomy for endometriosis and/or endometrioma were excluded. Surgical treatment consisted of thorough laparoscopic electrocauterization/ablation or excision of all peritoneal and nonperitoneal endometriotic lesions, lysis of adhesions, and appropriate management of ovarian endometriomas. Our patients were classified into 2 groups. Group 1 consisted of 23 patients with clinical symptoms of endometriosis and/or endometrioma, who received laparoscopic surgery with a modified IVF (GnRH antagonist) protocol at the same time (on the day of oocyte retrieval). Group 2 consisted of 24 patients with a previous history of laparoscopic surgery for endometrioma. After laparoscopic surgery (at least

3 months later), they tried to conceive through the traditional IVF treatment with a GnRH agonist protocol.

In our GnRH antagonist protocol, each patient received exogenous gonadotropins starting on the 2nd day of menstruation, and later, 0.25 mg/day of cetrorelix (Cetrotide, ASTA Medica, Halle, Germany; Baxter Oncology, GmbH, Germany) was administered subcutaneously, when the leading follicle reached 14 mm in diameter, until the human chorionic gonadotropin (hCG) injection. Patients who received the GnRH agonist protocol, were treated with 1 mg/day leuprolide (LEUpolide acetate; FAMAR L’AIGLE, Saint Remy Sur Avre, France) starting on the 21st day prior to menstruation for pituitary desensitization. When exogenous gonadotropins were started on day 2 of menstruation, the dose of leuprolide was decreased to 0.5 mg/day. It was administered daily until the day before recombinant hCG (Ovitrelle; Merck Serono S.P.A., Modugno, Italy) injection. Additional doses of recombinant gonadotropin, including recombinant FSH (Industria Farmaceutica Serono S.P.A., Modugno, Italy) and lutropin alfa (Luvris; Serono, Switzerland), were given to patients in each group if necessary. The FSH dose was adjusted individually, according to the response of the ovaries and serum estradiol concentrations. The cycles were cancelled when estradiol showed a plateau or decreased level, LH was > 12.1 mIU/mL, or progesterone was > 1.7 ng/mL during ovarian stimulation. When the leading follicle reached 18 mm in diameter, or at least two follicles were > 17 mm in diameter, 250 µg of recombinant hCG was administered subcutaneously. Either laparoscopic (Fig. 1) or transvaginal oocyte retrieval was performed 34–36 hours later. Embryos were cultured and transferred transvaginally on day 2–3 after oocyte retrieval. The luteal phase was supported with micronized vaginal progesterone, 600 mg/day, until the 10th week of gestation, in cases where a pregnancy was achieved.

Data regarding patient demographics, including age, parity, the numbers of oocytes retrieved, the numbers of embryos transferred, and the stages of endometriosis, were recorded in our retrospective study. The severity of endometriosis was classified into minimal, mild, moderate and severe stages according to the American Society for Reproductive Medicine (ASRM) revised classification of endometriosis. Positive



Fig. 1. Oocyte retrieval with the aid of laparoscopy in women with endometriosis.

chemical pregnancy is determined by a serum hCG > 30 mIU/mL. Clinical pregnancy is defined as the presence of a positive fetal heart beat detected by sonography. Live birth is defined as a live baby delivered after 24 weeks gestational age.

The statistical analyses were performed using the Statistics Package for Social Science version 11.0 (SPSS Inc., Chicago, IL, USA). The differences in the age, numbers of oocytes retrieved and the numbers of embryos transferred between the endometriosis study groups, were examined by the Student *t* test. The Fisher's exact test was used to analyze the pregnancy outcome amongst these two groups. Statistical significance was defined as $p < 0.05$. The power for detecting the statistical significance of live birth rate between minimal or mild (early-staged) and moderate or severe (advanced-staged) endometriosis is 0.67563. The power between minimal or mild (early-staged) endometriosis and IVF with previous laparoscopy for endometriosis is 0.66937 for live birth rate.

Results

In group 1, 23 patients (mean age = 34.78 ± 3.80 years; average numbers of oocytes retrieved = 5.09 ± 4.65 , average numbers of embryos transferred = 1.94 ± 0.77) who underwent a total of 23 assisted reproduction cycles, were recruited. These patients received laparoscopic surgery and IVF treatment at the same time. In group 2, 24 patients (mean age = 34.83 ± 4.33 years; average numbers of oocytes retrieved = 6.44 ± 5.14 , average numbers of embryos transferred = 2.04 ± 0.98) who underwent a total of 27 IVF cycles, were recruited. No statistical significance was noted between the two study groups regarding age, numbers of oocytes retrieved and the numbers of embryos transferred (Table 1).

Table 2 shows the results of pregnancy outcome in both groups. In group 1, 9 patients were diagnosed with minimal to mild endometriosis. Our results of the chemical pregnancy, clinical pregnancy and live birth rates obtained from these patients were 66.67%, 55.56% and 55.56%, respectively. Amongst the remaining 14 patients diagnosed with moderate and severe stage endometriosis, only one subject conceived successfully, and the results of the chemical pregnancy, clinical pregnancy and live birth rates obtained from these patients were all 7.14%. In group 2, 24 patients with endometriosis (post status laparoscopic surgery for endometrioma) received a total of 27 IVF cycles. Results for the chemical pregnancy,

clinical pregnancy and live birth rates obtained from these patients were 37.04%, 25.93% and 14.81%, respectively.

If we further compared the results obtained from Table 2, a statistically significant difference ($p \leq 0.005$) was noted in the chemical pregnancy rate between patients with minimal or mild stage endometriosis (66.67%, 6/9 patients) and patients with moderate or severe stage endometriosis (7.14%, 1/14 patients) in group 1 patients. The clinical pregnancy rate and live birth rate between these two groups also showed statistically significant differences ($p = 0.018$). If we compared the results of live birth rate between patients with minimal or mild stage endometriosis (66.67%, 6/9 patients) and patients with prior laparoscopic surgery for endometrioma, a higher live birth rate was achieved in group 1 patients with minimal or mild stage endometriosis ($p = 0.026$). Although the values of power calculation in live birth rates were both less than 0.8, statistically significant differences were noted from the above data.

Discussion

Endometriosis is considered to be a polygenic disease with a complex, multifactorial etiology [21]. Several studies have examined the association of endometriosis and implantation failure on a molecular level. These basic science studies suggest that endometriosis may be involved in the deregulation of selective genes which play critical roles in the process of implantation [22,23]. The optimal approach is to reduce inflammation in the pelvis, annihilate any adverse factors leading to endometriosis, and consider surgical treatment of endometriotic lesions, in order to create a conception friendly environment resulting in enhanced uterine receptivity.

The influence of endometriosis on IVF and the management before IVF remain controversial. The fertilization rate is reduced in endometriotic women with early stages (stage I and II), which may be due to a hostile microenvironment [24]. Poor IVF outcome is seen in endometriotic women with advanced stages (stage III and IV). In our study, patients with minimal or mild stage endometriosis, who received laparoscopic surgery together with IVF treatment simultaneously, had higher pregnancy rates than patients who suffered from moderate or severe stage endometriosis. Our study showed that patients who received laparoscopic surgery for endometrioma, followed by IVF treatment (group 2), usually suffered from moderate or severe stage endometriosis. Although different IVF stimulation protocols were used in our study, when comparing patients in group 2 with those moderate or severe stage endometriosis patients who received laparoscopic surgery together with IVF treatment in group 1, there was no difference in the pregnancy outcome between those two groups. However, when compared with patients in group 2, group 1 patients who suffered from minimal or mild stage endometriosis and received laparoscopic surgery and IVF treatment simultaneously, had higher live birth rates. There are comparable clinical outcomes for the GnRH antagonist and long GnRH agonist protocols for IVF treatment [25]. The use of antagonist protocols is associated with a reduction in

Table 1
Comparison of demographic data between IVF + simultaneous laparoscopic treatment and IVF + previous laparoscopy in women with endometriosis.

	IVF + simultaneous laparoscopy for endometriosis	IVF + previous laparoscopy for endometriosis	<i>p</i>
Patient no.	23	24	
Cycle	23	27	
Age (yr)	34.78 ± 3.80	34.83 ± 4.33	0.966
Egg no.	5.09 ± 4.65	6.44 ± 5.14	0.336
Embryo transfer (ET) no.	1.94 ± 0.77	2.04 ± 0.98	0.730

Table 2

Comparison of *in vitro* fertilization outcomes between IVF + simultaneous laparoscopic treatment and IVF + previous laparoscopy in women with endometriosis.

	IVF + simultaneous laparoscopy for endometriosis		IVF + previous laparoscopy for endometriosis
	Minimal or mild	Moderate or severe	
Chemical pregnancy rate	66.67 % (6/9)*	7.14% (1/14)	37.04% (10/27)
Clinical pregnancy rate	55.56 % (5/9)*	7.14% (1/14)	25.93% (7/27)
Live birth rate	55.56% (5/9)*	7.14% (1/14)	14.81% (4/27)

*Fisher's exact test, $p < 0.05$.

ovarian hyperstimulation syndrome, without a difference in live-birth rates. In addition, the pregnancy outcome may further improve by frozen embryo strategy, to offer better endometrial environment for implantation [26]. In patients with moderate or severe stage endometriosis in group 1, the embryo may be frozen after confirmation of fertilization. Because there is no significant difference in implantation or pregnancy rate of frozen thawed embryo transfer cycles following previous IVF GnRH agonist or antagonist stimulation [27], they could only stop embryo transfer in the fresh cycle and wait for the next suitable cycle to improve pregnancy outcome.

Laparoscopic surgery is indicated for infertile women with ovarian endometriomas with preservation of the normal residual ovarian cortex. Laparoscopic endometrioma cystectomy reduces the ovarian reserve, but does not impair the pregnancy outcome [28]. A reduced follicular response, in natural and clomiphene-stimulated cycles, has been shown in younger women after ovarian cystectomy for endometriomas, but can be recovered with gonadotropin stimulation [29]. In patients with advanced stages of endometriosis, a significantly poorer IVF outcome has been demonstrated as compared to those patients with tubal infertility [30]. Our previous study found that there were lower indices of intraovarian blood flow in endometriosis patients during IVF using power Doppler ultrasound analysis. The decreased ovarian vascularity in the ovarian endometrioma group, may be ascribed to intra-operative ovarian damage [31]. Surgery should be envisaged only in the presence of large cysts (balancing the threshold to operate with the cyst location within the ovary), or to treat concomitant pain symptoms which are refractory to medical treatments, or when malignancy cannot reliably be ruled out [18]. In addition, the experience of the laparoscopist may affect ovarian reserve in infertile women who previously underwent laparoscopic treatment for endometriomas, which leads to decreased antral follicle count number and live birth rate during IVF treatment [32].

Differences in the financial budget of medical insurances exist in different countries. The cost of operations is always expensive. It is also hard to classify the stage of endometriosis without further surgical intervention. In Taiwan, the cost of laparoscopic treatment for endometriosis is covered by National Health Insurance of the Republic of China. Thus, it is indeed cost effective and beneficial to perform laparoscopic surgery with modified IVF therapy simultaneously, as shown in the live birth rate results of our group 1 patients with minimal or mild stage endometriosis. In this study, we

attempted to overcome the obstacles of decreased ovarian reserve, ovarian response and increased morbidity in patients with ovarian endometrioma related infertility, via performing laparoscopic surgery and modified IVF treatment simultaneously. The pregnancy outcome did not demonstrate a significant difference between traditional IVF treatment in endometriotic women after laparoscopy and modified IVF with laparoscopy for ovarian endometrioma, although the traditional IVF GnRH protocol showed higher pregnancy rates. Therefore, individualized IVF protocols are tailored according to the patient's age, etiology of infertility (endometriosis related), duration, type and the results of previous IVF protocols. The optimal approach in managing an infertile endometriosis patient, is to perform a comprehensive evaluation, and then develop a treatment protocol that is individualized for each patient starting from a simple, safe, cost-effective treatment to a sophisticated and expensive treatment.

In conclusion, traditional GnRH agonist IVF protocols may assist in the pregnancy rates of women who suffer from moderate and severe endometriosis, confirmed from previous laparoscopic surgery. For those patients with minimal and mild endometriosis, laparoscopic surgery, combined with modified GnRH antagonist IVF cycles, would improve pregnancy rates, decrease morbidity and reduce unnecessary medical costs. In addition, it will shorten the time to conception, which is the optimal goal for an infertile couple and the surgeon. In our pioneer study, innovative protocols were applied in order to demonstrate the differences in fecundity rate in endometriosis-associated female infertility via a similar treatment strategy, but adjusted order of events in the treatment protocol. One shortcoming in our study was the limited number of patient. Further multicenter, randomized, clinical trials regarding this issue should be undertaken.

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