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Research Letter

A cumulative strategy of GnRH agonist, clomiphene citrate, and GnRH antagonist in a patient with recurrent endometriosis and repeated aspiration

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The prevalence of endometriosis may be up to 22% of asymptomatic women and 30% of women with infertility [1]. It is also estimated that 17–44% of all patients undergoing *in vitro* fertilization (IVF) have ovarian endometrioma [2,3]. The optimal treatment for endometrioma is still a controversial issue. Traditionally, the management approach toward endometrioma has been either surgical or hormonal. But, neither has a clear-cut advantage over the other in terms of reproductive success. However, whenever a patient is diagnosed as having ovarian endometrioma then surgery is advocated, as these persist despite hormonal treatment [4].

But, in the presence of pelvic adhesion or advanced stages of endometriosis, it can be difficult to identify anatomic structures, leading to suboptimal resectioning, frequent cyst recurrence, and surgical complications. Ultrasonic needle-guided aspiration of ovarian endometriomas was proposed in 1991 as an alternative for patients who had recurrent endometriomas or when surgery was contraindicated for medical or personal reasons [5]. In addition, the interest in cost-effective outpatient therapy and the expected difficulty in surgical treatment of recurrent endometriosis made the aspiration of endometrioma an option before ovulation induction. Though Pabbuccu et al. [6] reported that aspiration of endometriomas before controlled ovarian hyperstimulation (COH) neither reduced the amount of gonadotropins used nor increased the number of follicles and oocytes retrieved; Hsieh et al. [7] showed that following aspiration the number of antral follicles increased. It was also reported by Dicker et al. [8] that the pregnancy rate improved significantly after aspiration of endometriotic cysts before ovulation induction.

Though a pattern for poor responders with IVF is lacking, it has been reported that ovarian cystectomy reduced follicle and oocyte numbers in COH, and patients with compromised ovarian status had a reduced potential of oocyte recruitment [9]. Many strategies are available for the treatment of poor responders with varying degrees of success ranging from the unstimulated cycle to COH with clomiphene citrate, urinary and recombinant gonadotropins, and adjunctive gonadotropin-releasing hormone agonists (GnRHa) and antagonists (GnRH-ant) [10].

Here, we present a case of infertility with bilateral obstructive fallopian tubes and recurrent endometriomas. Before enrolling the patient for IVF, she was treated by repeated aspiration of recurrent endometriomas, then a cumulative strategy of COH regimen was applied for the IVF program.

A 32-year-old nulliparous woman presented with severe dysmenorrhea and infertility for 5 years. She gave a history of a previous conservative surgery 6 years ago for extensive pelvic endometriosis with a right ovarian endometrioma measuring about 9 cm × 9 cm in diameter. Transvaginal ultrasonography revealed the presence of bilateral adnexal cysts, 11 cm × 9 cm and 8 cm × 6 cm in diameter, with speckled homogenous echogenicity. Computed tomography examination revealed bilateral adnexal masses. After counseling, transvaginal ultrasonic needle-guided aspiration of 120 mL of chocolate-like material from the right ovarian cyst and 80 mL from the left ovarian cyst was performed.

Aspiration was done on a day care basis. The patient was given slow intravenous preoperative sedation, 50 mg of pethizine, and 10 mg of pentazocine just before starting the procedure. An ultrasound examination was carried out just before aspiration, and the optimal size for puncture was selected. Transvaginal ultrasonic needle-guided aspiration of the endometriotic cyst was done using a transvaginal transducer (5.5 MHz; Aloka, Tokyo, Japan), double lumens

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ovum pick-up needle (K-OPSD-1635-A-L, 16GA/35 cm; Cook, Brisbane, Australia), and suction unit (K-MAR-5100; Cook, Brisbane, Queensland, Australia).

The progress of the needle was observed through the tissue on the ultrasound until the tip was visualized well within the cyst. The needle tip was monitored throughout the whole procedure. As the endometritic cystic content was so thick, normal saline irrigation was carried out to complete aspiration. The aspirate was sent for cytological examination. After complete evacuation of the cyst, 95% ethanol was irrigated through the cystic cavity for 10 minutes. Thereafter, the patient was treated with oral contraceptive pills (OCP) to control the endometriosis.

Three months later, vaginal ultrasound follow-up revealed a recurrence of endometriotic cysts which had reached a size of 8 cm × 6 cm and 6 cm × 6 cm in diameter. The patient was counseled again for reaspiration, then COH for IVF was started in the same cycle after the procedure.

The COH for IVF was the low-dose ultrashort GnRHa, clomiphene citrate, and gonadotropins with multidose of GnRH-ant protocol, and entailed the administration of 0.1 mg buserelin acetate (Supremon; Hoechst AG, Frankfurt an Main, Germany) subcutaneously for 3 days, starting on Day 2 of the menstrual cycle and clomiphene citrate, 150 mg (Clomid; Serono Laboratories, Rome, Italy), starting on the same day (Day 2) for 5 days. Recombinant follicular stimulating hormone 150 IU (Gonal-F; Serono Laboratories, Rome, Italy) and human menopausal gonadotropin 150 IU (HMG, Menopur; Ferring Pharmaceuticals, GmbH, Germany) were started on Day 3 of the menstrual cycle and continued according to the ovarian ultrasonic response. After the leading follicle had reached a size of 14 mm, co-treatment was initiated with the GnRH-ant (Orgalutron; Organon Ltd., Swords, Co. Dublin, Ireland) at 0.25 mg per day, which was continued up to and including the day the recombinant human chorionic gonadotropin (rhCG, Ovidrel; Serono Laboratories, SA, Aubonne, Switzerland) was injected. Folliculometry was performed by using transvaginal sonography (Aloka, Tokyo, Japan) equipped with a 5-MHz vaginal annual array transducer. When two or more follicles had reached a diameter of 18 mm, 10,000 IU of rhCG was given. Follicular aspiration was performed transvaginally under ultrasonar guidance 36 hours after rhCG administration, and oocytes were fertilized through conventional IVF. Two oocytes were aspirated and two embryos were transferred into the uterine cavity transvaginally 72 hours after ovum pick-up. Micronized progesterone 600 mg/d (Utrogestan, Laboratories Piette International SA, Brussels, Belgium) was administrated after ovum pick-up and rhCG 1500 IU subcutaneous injection was given every 3 days for a total of three doses after the embryos were transferred.

The progestin luteal support was continued up to 12 weeks of gestation. The patient is now going through singleton gestation.

Ovarian endometriotic cysts might decrease the success of COH and IVF because of the mechanical effect in which the ovarian cyst physically reduces the space for more follicles to develop.

The mechanical effect of the mass on the ovarian blood supply may result in poor ovarian response. In addition, the ectopic endometrial tissues impair the normal intraovarian mechanism of follicle and oocyte maturation, which in turn may affect the quality of the oocyte retrieved [11]. During ovulation induction, the presence of these cysts could make the ultrasound monitoring of follicular growth difficult, the retrieval of ovum more difficult, and in some cases the ovary inaccessible [5,12–14].

Furthermore, women with severe endometriosis may perform poorly in an IVF treatment program [14]. Somigliana et al. [15] reported that the presence of ovarian endometrioma is associated with a reduced responsiveness to gonadotropins. This deleterious effect was more evident in women with larger cysts and in those with more than one cyst. Suzuki et al. [16] also showed the numbers of retrieved oocytes were fewer in patients with ovarian endometrioma than in those with a tubal factor without endometriosis.

Laparotomy is still the conventional treatment of endometriosis and involves the drainage and removal of the cystic wall. There is evidence that excisional surgery of endometrioma provides for a more favorable outcome than drainage and ablation with regard to recurrence of the endometrioma, recurrence of pain symptoms, and in women who were previously subfertile, subsequent spontaneous pregnancy [17]. But, in some patients, operative laparotomy or laparoscopy may be contraindicated because of previous surgery and/or adhesion [5,18]. Recurrent endometriomas after laparoscopic or conservative open surgery for endometriosis is a more difficult clinical problem for those patients who wish to retain their fertility potential. The surgery often results in inadvertent removal of normal ovarian tissue, which may decrease the number of oocytes available for subsequent fertility treatment [19].

It has been reported that previous ovarian surgery might damage ovarian reserve, resulting in poor ovarian response and increased cancellation rate during COH for IVF [20]. It also has been shown that ovarian surgery of cystectomy has an adverse effect on ovarian response to stimulation with gonadotropins and thus on the results of fertility treatment [21]. Hachisuga and Kawarabayashi [22] reported that removal of the capsule of endometrioma was associated with loss of follicles and damage to the ovarian stroma. Nargund et al. [23] suggested that ovarian cystectomy reduced follicle and oocyte numbers in ovulation induction cycles, and the removal of endometrioma caused more damage to the ovaries than the removal of a simple cyst. In addition, a second operation is seldom effective in preventing recurrence of endometriosis following an unsuccessful or incomplete first operation [24].

As the management of endometrioma in infertile women before IVF remains controversial, the management of women with endometrioma before IVF should be individualized [18]. In spite of the aspiration of ovarian endometrioma having the disadvantage of a high recurrent rate [25], if fertility is the aim, aspiration might be a reasonable alternative to ovarian surgery to decrease the risk of cancellation during COH because of poor response in IVF protocol.

It has been reported that use of the transvaginal aspiration of pelvic cysts before COH may improve the outcome of IVF [12], and a significantly higher number of oocytes were recovered following aspiration in COH of IVF program [21]. Chang et al. [26] suggested that patients who underwent aspiration and sclerotherapy for recurrent endometriomas, resulted in the reduction of cystic size and preservation of more ovarian tissue made a significant improvement in folliculogenesis. Chang et al. [7] also found that the number of antral follicles increased in patients with aspiration and sclerotherapy with 95% ethanol for treatment of recurrent ovarian endometriomas. Sclerotherapy may help to preserve primordial follicles in a population already at risk of decreased ovarian reserve [18]. Thus for this recurrent endometrioma patient who wished to have COH for IVF performed, we used transvaginal ultrasonic needle-guided aspiration of the endometriotic cysts as an optimal line of treatment.

The treatment of low responders with IVF remains a challenge, and it is extremely important to identify these patients before initiation of COH for IVF. Many strategies are available for the treatment of poor responders, including increasing the dose of used gonadotropins, using GnRH-ant, reducing or discontinuing the dose of GnRHa, initiating GnRHa and gonadotropins together in the follicular phase (the so-called ultrashort or short flare protocols), and using a microdose GnRHa flare protocol [9,10,27].

Nevertheless, no compelling advantage has been established for one stimulation protocol over another [28]. Bergen et al. [29] reported that combining the microdose flare GnRHa and GnRH-ant protocols in poor responders who previously had failed several IVF treatment cycles resulted in an acceptable clinical pregnancy rate. Orvieto et al. [28] reported a COH protocol, which included ultrashort GnRHa combined with GnRH-ant resulted in a higher number of oocytes and top-quality embryos than the patient's previously failed IVF attempt. D'Amato et al. [30] proposed a protocol of COH with GnRH-ant, high dose recombinant follicular stimulating hormone, and clomiphene citrate for poor responders and obtained lower cancellation rates and higher oocyte retrieval, implantation rates, and pregnancy rates.

In the present case, we used a cumulative strategy protocol of COH for the potentially low-responder patient to increase endogenous gonadotropin and estradiol secretion, and avoid premature luteinizing hormone (LH) surges. We combined the beneficial effects of OCP pretreatment, the clomiphene citrate, and the low-dose ultrashort GnRHa with that of the GnRH-ant. First, pretreatment with OCP was shown to synchronize follicular development and eliminate the existing corpus luteum and restore sensitivity in the ovarian follicles to exogenous FSH [31,32]. Second, clomiphene citrate administration in the early follicular phase, which stimulate gonadotropins release at the pituitary level (flare effect) and estradiol secretion from granulosa cells [33]. Third, following the clomiphene citrate and HMG treatment there was a lower rate of fracture zona oocytes, higher rates of fertilization, and normal growth of fertilized eggs [34].

The low-dose ultrashort GnRHa protocol provokes secretion of gonadotropins in the early follicular phase [35]. But, Hazout et al. [36] observed that the 3-day ultrashort GnRHa/HMG protocol did not reliably prevent premature LH surges and so some premature LH surges may occur. The addition of GnRH-ant to ovarian stimulation during the late follicular phase will prevent premature LH surges while not causing any suppression in the early follicular phase, which is a critical period of patients with decreased ovarian reserves [37]. Moreover, GnRH-ant provides immediate LH suppression with the possible improvement of the generated embryo [29].

In conclusion, for the purpose of reducing the sequels of operative laparoscopy or laparotomy of ovarian endometrioma, transvaginal ultrasonic needle-guided aspiration was used as an alternative for the management of recurrent endometrioma. The procedure is simple, safe, and repeatable in the treatment of selected cases of endometrioma. We also proposed a cumulative strategy COH protocol entailing the use of clomiphene citrate, gonadotropins, low-dose ultrashort GnRHa, and multiple doses of GnRH-ant to the potentially poor responder.

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