Does Ovarian Reserve Change after Endometrioma Management? Comparison of Two Treatment Regimens

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Abstract

Background: The endometriosis-mediated damage to ovarian reserve beyond the stretching of ovarian cortex that can lead to loss of primordial follicles is supported by many studies.Laparoscopy represents the first-line treatment in sub fertile women with endometriotic ovarian cysts. The primary benefit of surgical treatment of endometriosis is the relief o f pelvic pain. The effect of laparoscopic cystectomy of an endometrioma on the antral follicle count has been conflicting.

Objective: is to estimate effects of laparoscopic ovarian cystectomy on ovarian reserve and ICSI outcome.

Methodology: 100 patients with unilateral ovarian endometrioma (size from 2.5-5 cm) were selected for ICSI, divided into two equal groups, group1 (underwent laparoscopic cystectomy) and group2 (underwent ultrasound guided cyst aspiration). Both groups were compared regarding ICSI outcome (number of oocytes, number of embryos transferred, pregnancy rate) as well as change in AMH as a marker of ovarian reserve 6 months after the procedures. Outcome measures: the outcomes were the ovarian reserve changes after the two procedures as well as the Intracytoplasmic Sperm Injection outcomes.

Results: There is a remarkable reduction in the level of AMH in group1(43% reduction) compared to group2 (5.7%) with no significance (P=0.393).

Conclusion: In view of the hazardous effect of laparoscopic ovarian cystectomy on ovarian reserve, ultrasound guided aspiration may be a good alternative procedure for treatment of endometrioma in view of preserving the ovarian tissues without compromising ICSI outcomes.

INTRODUCTION

The pathogenesis of typical ovarian endometriosis is a source of controversy. Hughesdon demonstrated, by serial section of ovaries containing an endometrioma, that 90% of typical endometriomas are formed by invagination of the cortex after the accumulation of menstrual debris from bleeding of endometrial implants, which are located on the ovarian surface and adherent to the peritoneum [1].

It was recently demonstrated that decreased follicular density, associated fibrosis, and deterioration of normal structure of ovarian cortex in ovaries that are affected by endometriomas[2]

The endometriomas themselves are the cause of diminished ovarian

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reserve in women with endometriosis. Deterioration of ovarian reserve may precede surgery and destructive surgery may exacerbate their reproductive potential further [2]

Endometriomas often present on ultrasound as cystic structures with low-level homogenous internal echoes consistent with old blood, and occasional thick septations, thickened walls, and echogenic wall foci [3]

Laparoscopy is the gold standard for the diagnosis of endometriosis[4]

In addition to perfect diagnosis of endometrioma, laparoscopy can identify the pelvic endometriosis that could not be diagnosed by ultrasound. However, laparoscopy is an invasive technique.

Whether the presence of endometrioma affecting the oocyte quality or not is a matter of controversy. In the study by Filippi et al., they showed that the presence of ovarian endometrioma does not affect oocyte quality[5]

Despite that, and in view of the follicular number, several studies have shown that there is a loss of follicular density in ovaries with endometriomas compared with unaffected ovaries [6],[7]

Many publications have raised concern over the deleterious effects of laparoscopic ovarian cystectomy on ovarian reserve, specifically as reflected by anti-Mullerian hormone (AMH) levels [8]

Ultrasound guided aspiration of endometriomas has an application in patients who are not good surgical candidates or who have experienced in vitro fertilization (IVF) failure, it is considered relatively safe and noninvasive [9]

Even in patients who are good surgical candidates for laparoscopy, this study was conducted to test the hypothetical value of ultrasound guided cyst aspiration as an alternative option for laparoscopic cystectomy in view of preserving the ovarian tissue without compromising the intra cytoplasmic sperm injection (ICSI) outcome.

Methodology

This is a retrospective cohort study that performed in ART unit, Al-Azhar University and including 100 patients with endometrioma and indicated for ICSI in the period from July 2013 to September 2015. They were divided into two equal groups, group1 (no.=50 patients) underwent laparoscopic ovarian cystectomy (LC) and group2 (no.=50 patients) underwent ultrasound guided aspiration followed by a proper antibiotic to guard against pelvic infection. The study was approved by the University Medical Ethical Committee. The patients have the following criteria:

Inclusion criteria

- Patients age less than 35 years,
- Body mass index (BMI) ≤30
- Unilateral endometrioma with size between 2.5 – 5 cm.
- Basal hormonal levels of FSH, LH in the early follicular phase of < 10 IU

Exclusion criteria

- Patient with other pelvic pathology as uterine myoma or other ovarian cysts.
- Patients with history of previous ovarian surgery or exposure to radiation or chemotherapy for malignant conditions.

In group I, under general anesthesia, laparoscopic cystectomy was performed at midcycle(KARL STORZ SE & Co. KG, Tuttlingen, Germany).After inspection of the intra-abdominal area and obtaining peritoneal washing, mobilization of the ovaries was done. The utero-ovarian ligament is taken with a 5-mm atraumatic grasper. Lysis of the adhesions is performed with the use of sharp dissection to fully mobilize the ovaries. Adhesiolysis was performed by scissor and in some cases cauterization with scissor was needed. In most cases, the cyst was ruptured during mobilization of the ovary, which required the liquid to be aspirated immediately to prevent pelvic contamination .The cysts were enucleated with their capsules (with cauterization of the bleeding points by bipolar electrocautery when needed). Ovarian stimulation was conducted in the next cycle.

In group II, and after intravenous sedoanalgesia using a combination of 25 mg of pethidine hydrochloride and 50 mg of fentanyl,ultrasound guided cyst aspiration(using Cook aspiration needle 16 gage ,30 cm length, single lumen needle,Cook Group Company,Indiana,USA)and under 200 mm Hg negative vacuum pressure was carried out premenstrual just before stimulation.

Ovarian stimulation: Patients in both groups were received short protocol with short acting s.cGnRH agonist (0.1 mg triptoline) daily starting from the first day of the cycle. 225 IU of recombinant fsh (rec.fsh) was administered from the second day of the cycle. Treatment with rec-fsh and GnRH agonist continued daily. The dose of stimulation was adjusted after Day 5 of stimulation, depending on the ovarian response, as assessed by estradiol (E2) levels and ultrasound. As soon as at least three follicles reached a mean diameter of >17 mm, 10000 IU of human chorionic gonadotrophin (hCG) was administered i.m.

Oocyte retrieval, embryo transfer, luteal support: Oocyte retrieval was performed 35-36 hours after the hCG injection by transvaginal ultrasound-guided double lumen needle aspiration under 100 mm Hg vacuum pressure. Ultrasound guidance was used for all embryos transfer, which was performed 2 or 3-days post-oocyte retrieval. Oocyte quality and embryo grading were determined.

Ultrasound and laboratory assays: All ultrasound measurements were performed using a 7.5 or 6 or 5 MHz vaginal probe. AMH, FSH, LH, E2 and prolactin levels were measured at the preceding cycle day2 using ELFA technique (Enzyme linked Fluorescent Assay, VidasBiomerieux) and AMH was repeated 6 months after the procedure in both groups for the non-pregnant cases

Outcome measures: the primary outcome measure was the ovarian reserve changes presented by the changes in estimated AMH levels in both groups. Secondary outcome measures were the clinical pregnancy rate per patient randomized, numbers of oocytes retrieved, number of metaphase II oocytes, fertilization rate, pregnancy rate and recurrence rate. AMH was measured before the procedures and 6 months after the ICSI trials for non-pregnant cases.Data was collected and refined using Microsoft Excel 2013 (Microsoft Corporation, USA).Data were analyzed using the Statistical Program for Social Science (IBM SPSS Statistics 20). Quantitative data were presented by mean± standard deviation (SD) and qualitative data were presented by frequency and percentage. P value was considered significant if < 0.05.Student-t test was used for estimating the difference between 2 independent quantitative samples .Chi-square test was used for comparison of qualitative data. Sample size was calculated using Epi-info 7 for Windows with the power of the study =80%, the level of significant to be 5% and the effect size that gave the minimal clinical difference reported from previous reviews.

Results

Table (1): The basal characteristics of the studied patients.

	Group I (n = 50)		Group II (n= 50)		
	Mean	**±SD**	**Mean**	**±SD**	**p-value***
Age (years)	29.8	3.1	29	3.9	0.326
BMI	28.1	2.1	27.3	2.8	0.088
FSH	5.6	1.6	6.2	2.4	0.175
AMH	3.2	0.8	3.5	0.6	0.814
LH	4.2	1.7	4.5	2.1	0.400
re FSH dose	3625	1299.3	3423	1168.6	0.416
Duration of stimulation	10	2	10	1.6	0.869

*Independent Sample t-test was used for comparison between quantitative variables.

This table shows no statistically significant difference between groups according to age, BMI. Basal hormones (FSH and LH), re FSH dose and duration of stimulation

Table (2) Comparisons between both groups regarding the secondary outcomes.

Parameter	Group1	Group2	P-value
Number of oocytes retrieved(mean ±SD)	6.7± 2.7	5±2.8[1]	**0.003***
Number of MII oocytes(mean ±SD)	2.8± 1	1.9±0.7	**0.370**
Number of Embryos transferred(mean ±SD)	1.8± 0.7	1.7± 0.9	**0.750**
Fertilization rate (%)	53.1%	50%[2]	**0.857**
Pregnancy rate (%)	34%(17/50)	38% (19/50)	**0.842**
Recurrence rate (%)	12%(4/33)	38%(12/31)	**0.6292**

[1] Independent Sample t-test was used for comparison between quantitative variables.
[2] Chi-square test was used for comparison between qualitative variables.
*The level of significance if p-value ≤.05

There is statistically significant differences between groups in view of number of Oocytes retrieved, it is higher in group 1 than 2.On the other hand there are no statistically significant differences between groups in view of number of MII oocytes, number of embryos transferred, fertilization, pregnancy and recurrence rates.

Table (3): The levels of AMH estimated in the same group before and after procedures.

AMH	Before procedure	After procedure	P-value*
Group I (laparoscopic ovarian cystectomy) (no=33)	3.2± 0.8	1.8±0.6	0.394
Group II (ultrasound guided cyst aspiration) (no=31)	3.5 ± 0.6	3.3 ± 0.9	0.842

*Paired t-test was used for comparison

There is no statistically significant difference according to (AMH) estimated before and after procedure in both groups with (mean ±SD 3.2±0.8 vs 1.8±0.6 with p =0.394) for group1 and (mean ±SD 3.5±0.6 vs 3.3±0.9 with p =0.842) for group2.

From the above table we can calculate the reduction rate for AMH in both groups as shown in figure(1).

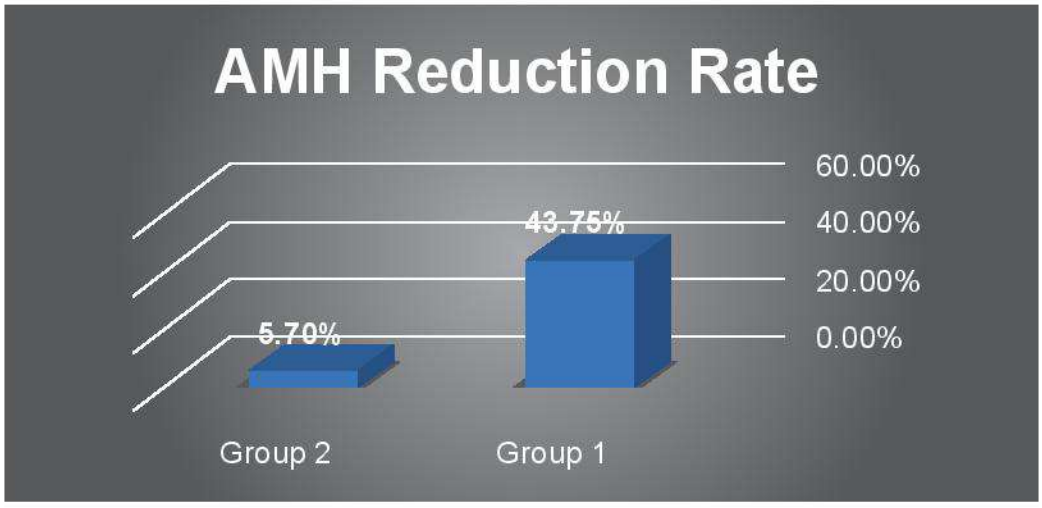

Figure (1): Bar chart presents AMH reduction rate in both groups, 6 months after the ICSI trials in non-pregnant cases.

The reduction rate was calculated by estimating the change in AMH levels before and after the procedures in both groups.

Table (4) comparison of AMH (in both groups) estimated 6 months after the procedures.

Parameter	Group1(no.=20)	Group2(no.=22)	P-value*
AMH (mean ±SD)	1.8±0.6	3.3 ± 0.9	**.187**

*Independent sample t-test was used for comparison.

There is no statistically significant difference between the two groups in view of the levels of AMH estimated after procedures, with p-value =0.187

Discussion

The detrimental effects with endometriosis-associated infertility patients offered ART present poor ovarian response [10], [11] ,lower fertilization rates[11] ,[12], decreased endometrial receptivity [13], and poor implantation rates[14]. It has also been suggested that oocyte and embryo quality [15],may be compromised in patients with endometriosis. It has also been reported that the incidence of aneuploidy is significantly higher in patients with endometriosis [16]

This study was designed to evaluate the ovarian reserve changes after two treatment regimens for 100 patients with ovarian endometrioma with sizes from 2.5-5cm (laparoscopic ovarian cystectomy, and ultrasound guided cyst aspiration) in addition to the estimation of outcomes of ICSI.Patients with endometrioma>5 cm was excluded from the study because of the higher recurrence rate reported by many studies.

Two groups were compared (50 patients in each group) and the data was analyzed anonymously.

The study showsno significant difference between groups in view of the basal characteristics (Age,BMI, FSH,AMH, LH, stimulation dose, duration of stimulation).

There is a significant difference between both groups in view of the numbers of oocytes retrieved(mean ±SD 6.6±2.7.and 5.0. ± 2.8 with P-value=0.0.03).This is may be explained by the relieve in the ovarian tissue produced by the excision of the cyst that allow the ovary to be more responsive and not compromised by the recurrent cysts or the remaining endometrial tissues.However, there is no significant difference between both groups in view of Oocyte quality (mean ±SD 2.8±1.and 1.9. ± 0.7 with P-value=0.370), for numbers of metaphase II (MII) Oocytes in group1 and group 2 respectively.

In addition to that, the study reported no significant difference between groupsin view of the numbers ofembryos transferred(mean ±SD 1.8±0.7.and 1.7± 0.9 with P-value=0.0.455), in both groups. The pregnancy rates did not differ significantly between the two groups (34% versus 38% with P-value=0.677).

For that, the need for effective treatment that can eliminate the associated negative effect of endometriomas on the ovaries as well as relieving the distressing symptoms associated with them i.e. dysmenorrhea, dyspareunia and non-menstrual pelvic pains is of mandate.

Surgery for the ovarian endometrioma is efficacious when pain or infertility is present [17]

Many studies consider Laparoscopy as the gold standard for treatment of ovarian endometriomasin many aspects associated with a shorter hospital stay, faster patients' recovery, decreased costs and a lower incidence of post-operative adhesion formation.

The presumptive benefit of LC to reduce or reverse the inherently damaging effects of endometriomas on the ovarian cortex is more controversial. The endometriosis-mediated damage to ovarian reserve beyond the stretching of ovarian cortex can lead to loss of primordial follicles[18]

Despite that, electrocoagulation after laparoscopic excision of ovarian cysts is associated with a statistically significant reduction in ovarian reserve, which is partly a consequence of the damage to the ovarian vascular system [19]

Because the preservation of the vascular blood supply to the ovary is vital for the preservation of ovarian volume and antral follicular counts. Meticulous surgical techniques, avoiding the compromise of ovarian blood supply and healthy ovarian tissue are of great importance.

In the study by Donnez et al, they described a new mixed technique for the laparoscopic management of endometriomas that can preserve the damaging effects following the removal of endometrioma, summarized in the following steps:

1. The endometrial cyst is opened and washed out with irrigation.
2. The inner lining of the cyst is stripped from the normal ovarian tissue.
3. If the excision provokes bleeding, or if the plane of cleavage is not clearly visible, the cystectomy is stopped because of the risk of removing normal ovarian tissue containing primordial, primary, and secondary follicles along with the endometrioma.
4. The cyst wall should be removed up to the hilus (partial cystectomy)
5. CO2 laser is used to vaporize the remaining 10%–20% of the endometrioma close to the hilus.
6. Don't close the ovary after the operation[20]

The possibility of a reduced ovarian reserve should be discussed with the patient, but this issue should not however change the well-defined indications for surgery.

The advantages of U/S guided aspiration of endometriomas, it is easily performed, and patients can return to normal activities shortly following the procedure [21]

In agreement with the results of the current study except for the number of oocytes retrieved, a meta-analysis by *Tsoumpou et al.,* found no significant difference in the dosage of gonadotropins used, oocytes retrieved, embryos available for transfer, or clinical pregnancy rates between ultrasound guided cyst aspiration and surgical intervention[22]

In a study by *Hamdan et al*, includedwomen with endometrioma underwent laparoscopic cystectomy compared with who had transvaginal aspiration. They reported that women had a similarclinical pregnancy rate (CPR)and similar total (FSH dose)[23].This also matched with the results of the current study.

In contrary to the results of this study, a prospective study comparing operated and aspirated ovaries in women who previously underwent laparoscopic cystectomy of endometriomas, Ragni et al., did find a lower number of developing oocytes and retrieved oocytes from the operated ovary. However, there was no difference in fertilization rates or high-quality embryos in these women [24]

AMH is considered the most reliable non-invasive methods of ovarian reserve evaluation [25].In the meta-analysis performed by ***Raffi et al.*** 2012[26] a statistically significant fall of 38% for AMH levels was reported after excisional surgery, with a weighted mean difference of −1.13 ng/ml

In the current study, AMH was measured before and 6 months after the procedures to allow for complete resolution and restoration of the ovarian functions, so the comparison could be meaningful. After exclusion of pregnant cases in both groups, the number of patients who submitted to follow up by AMH level estimation were 33 cases in *group 1* and 31 cases in *group 2*.

There is a non-significant difference in means of AMH estimated before ICSI and 6 months after (means ± SD, 3.2± 0.8 Vs 1.8±0.6 with p-value=0.394) after LC.

Also after ultrasound guided cyst aspiration, there is a non-significant difference in means of AMH estimated before ICSI and 6 months after, (means ± SD, 3.5 ±0.6 vs 3.3 ± 0.9 with p=0.842).

There is a great reduction in the level of AMH in group1(43.75% reduction) if compared to the reduction in group2 (5.7%) with no statistically significant difference (P =0.393). The non-significant difference may be explained by the low number of cases in both groups who were submitted to follow up.

Whether this reduction is consistent and true is a matter of controversy. Rustamov et al reported that the association between surgery and decreased ovarian reserve as evaluated by AMH,is still inconclusive[27]

Muzii et al, 2011, [28]alsoreported that the damage to ovarian tissue is already present before surgery due to the disease itself, and not due to the surgical procedure.

Systematic reviews on AMH as a marker for the reduced ovarian reserve have highlighted the heterogeneity of the published studies and the difficulty in pooling the data[26]

In addition to that, AMH may reflect an immediate insult to the residual ovarian tissue after surgery, which sums up with the ovarian damage provoked by the endometrioma itself[29]

Although, the risk of surgery on endometrioma is rising, it may be to a certain extent, only temporary, and, in fact, a partial recovery has been reported by some authors at longer follow-up times[30]

AMH may recover 3 months postoperatively or may be sustained up to 6 months, even in the hands of experienced laparoscopic surgeons[31]

In a contradiction to the above studies, Uncu et al. demonstrated that surgical excision of endometriomas leads to a decline in AMH that appears progressive[32]

Recurrence rates among both groups after 6 months were 12 % (4 cases out of 33) for group1 and 38 % (12 cases out of 31) for group2 with P-value=0.0.6292) without significant difference between both groups.

This recurrence may be explained by incomplete removal of the cyst bed or with high grades of endometriosis or effect of ovarian stimulation in both groups.

The main problem related to the cyst aspiration is the high rate of recurrence following the procedure. For prevention of the recurrence, measures in the form of post-operative hormonal therapy was suggested by many authors, but the results were inconclusive as reported by the study of Sesti et al 2009[33]

Recurrent endometriomas, as detected by TVS, can remain asymptomatic and do not necessarily progress in size with or without medical treatment. The decision to re-operate depends less on the endometrioma's size than on symptoms. However, such patients are also more likely to have signs of deep nodules and adnexal/bowel adhesions and larger endometriomas on TVS scan, thus predisposing them to require a second procedure [34].

In spite of all these results, debate will continue regarding the decision for endometrioma management especially that with sizes more than 3 cm. We think that this debate is logic and may be explained by the differences in patients´ history, symptoms and indications for treatment. All these factors should be taken in considerations before decision. We think that large randomized controlled trials in the futures with further reviewing may give an evidence that may resolve this conflict. Also the pain assessment after both procedures should be discussed in the future studies because it may give a good hint about which procedure may be superior in view of symptoms management.

Conclusion

The oocyte yield after laparoscopic cystectomy for endometrioma is shown to be significantly better than ultrasound guided cyst aspiration. Also the tragic effect of laparoscopic ovarian cystectomy on ovarian reserve is not evident and more clinical trials were recommended to evaluate this effect. However, the cyst aspiration may be a good alternative tool that can replace the laparoscopic cystectomy, in view of preservation of ovarian tissues without compromising the ICSI outcomes.

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