ORIGINAL ARTICLE

Endometrioma and ART: Does the Needle Work?

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ABSTRACT

Aim and Objectives: The aim of this study was to see if the fertility outcome improved when IVF/ICSI was done after administration of GnRH analogs and cyst aspiration in comparison with patients in whom either only cyst aspiration or only GnRh analogs were administered.

Materials and methods: This was a prospective study done in a tertiary level ART center which included 30 patients over a span of 5 years from 2004 to 2009. All of them had endometriomas and underwent assisted reproductive techniques (ART) either after cyst aspiration with or without GnRH analog pretreatment or only GnRH analog pretreatment.

Depending on the pretreatment received, they were classified into three groups:

- Group B: Both GnRH analog and cyst aspiration
- Group C: Only cyst aspiration
- Group G: Only GnRH analog.

The patients were not randomized.

The number of days required for stimulation, total dose of stimulation required, number of oocytes obtained, quality of embryos, and the pregnancy rates for each group were tabulated for comparison.

Statistical analysis: The significance of the difference in ART outcome after the different modalities of pretreatment, which was estimated in terms of pregnancy rates was evaluated by calculating the p-value.

Observations and results: Significant difference was observed between the pregnancy rates in the three groups, with the maximum pregnancy rate in group B, followed by the group G and then the group C. The p-value showed a trend, though not statistically significant, indicating the need for larger prospective studies with greater number of subjects.

Conclusion: Pretreating endometriomas by aspirating the cysts and administering three doses of GnRH analog depot preparation prior to IVF/ICSI seems to be better than administering GnRH analog depot preparation alone or aspirating the cysts alone in terms of the number of days required for stimulation, the number of oocytes obtained, and the clinical pregnancy rates.

Keywords: Endometrioma, Cyst aspiration, GnRh agonist, *In vitro* fertilization.

INTRODUCTION

Endometriosis is a common gynecological condition, which affects approximately 10% of women of reproductive age. There is a range of symptoms, and most commonly women present with dysmenorrhea, pelvic pain, infertility or a pelvic mass. Direct visualization and biopsy during laparoscopy or laparotomy is the gold standard diagnostic test for this condition and enables the gynecologist to identify the location, extent and severity of the disease. The term chocolate cyst was used by Sampson in 1921 to describe an endometriotic cyst of the ovary and now, chocolate cyst and endometriotic cyst are used interchangeably. The most typical lesions in ovarian endometriosis are either surface deposits or endometrial cysts (endometriomas). The presence of a chocolate cyst indicates a more advanced stage of endometriosis.[2] Today, the revised American Society for Reproductive Medicine classification of endometriosis is widely accepted[3] for staging endometriosis. It takes into account the extent of disease, presence or absence of adhesions and the severity of adhesions. In this system, endometriosis is classified as stage 1 (minimal), stage 2 (mild), stage 3 (moderate), or stage 4 (severe). The diagnosis of ovarian endometrioma is usually based on visualization of cyst at a baseline transvaginal ultrasound or during a diagnostic laparoscopy. The sensitivity and the specificity of endovaginal ultrasonography in differentiating endometriomas from other ovarian cysts were 83 and 89% respectively. This specificity (89%) is comparable with that obtainable with magnetic resonance imaging (91%).[4] Laparoscopy has a sensitivity of 97%, a specificity of 95%, and an overall accuracy of 96%. At times the Ca 125 marker may also be elevated. Aspiration of the chocolate-colored fluid at ultrasound-guided transvaginal aspiration or at laparoscopy, with histologic confirmation will help in arriving at a diagnosis. The presence of chocolate-colored fluid may be misleading because this fluid can also be

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found in other cysts, such as lutein cysts and even some neoplastic cysts.[5] But, however, histologic confirmation ascertains that it is an endometrioma and increases the sensitivity and specificity to > 95%.

AIM AND OBJECTIVES

To evaluate the role of endometrioma in assisted reproductive techniques (ART) and to compare the outcome of ART in patients with endometrioma after cyst aspiration or GnRH analog pretreatment or both and to ascertain which of the three modalities of pretreatment offers the best outcome in terms of pregnancy rates and to see if the fertility outcome improved when IVF/ICSI was done after administration of GnRH analogs and cyst aspiration in comparison with the contrary, in which either only cyst aspiration or only GnRH analogs were administered.

MATERIALS AND METHODS

This was a prospective study done in a tertiary level ART center, which included 30 patients over a span of 5 years from 2004 to 2009. All of them had endometriomas and underwent ART either after cyst aspiration or GnRH analog pretreatment or after both the modalities of pretreatment. Depending on the pretreatment received, they were classified into 3 groups:

- Group B: Both GnRH analog and cyst aspiration
- Group C: Only cyst aspiration
- Group G: Only GnRH analog depot preparation.

The patients were not randomized.

None of the patients in group C had reduced ovarian reserve, but, however the mean AFC in group C was lesser than that in group B and G. Mean AFC in group C = 7.8, group B = 8.6, group G = 8.3. None of the patients had FSH > 10.

The GnRH analog depot preparation used by us was Zoladex, manufactured by AstraZeneca Pharmaceuticals (Pvt) Limited, 5 Leeuwkop Road, Sunninghill-215. The depot preparation contains 3.6 mg of Goserelin acetate, which is supplied in a preloaded single-dose disposable syringe applicator, which is to be stored in the sealed package at a temperature below 25°C. The registration number of the product is U/21.10/163.

All the patients recruited in the study had undergone laparoscopy earlier and a laparoscopic diagnosis of endometriosis was made in all the patients.

The patients in group G had small cysts for which cyst aspiration was not done. But however, they had endometriotic deposits in the ovary for which they were classified as having severe endometriosis as per the revised ASRM classification of endometriosis. The outcome was compared taking into account the similar staging of endometriosis. None of the patients had undergone more than one laparoscopy.

Long agonist protocol was used in all the patients in group C except 2, in whom the antagonist protocol was used. However, despite comparable ovarian reserves, the duration of stimulation and the total dose of gonadotropins was found to be lesser in group B than group C.

Patients with endometriosis diagnosed by laparoscopy who opted for IVF/ICSI after repeated IUI failures were all scanned on the second day of the menstrual cycle intended for IVF/ICSI. Transvaginal sonography was done with 7MHz probe. The sonographic criteria for the diagnosis of endometrioma were presence of a cystic structure with low, homogeneous echogenicity and a thick cystic wall with regular margins. One important criterion for diagnosis of chocolate cysts by ultrasonography was the persistence of a cyst for at least two consecutive cycles.[6] This permitted us to distinguish a corpus luteum cyst from an endometrioma. Corpus luteum cysts, whose sonographic patterns are usually different from those of endometriomas, should regress spontaneously at the end of the menstrual cycle. A corpus luteum cyst looks somewhat like an octopus, in that the center is occupied by a blood clot and some highly echogenic branches ramify into the cystic fluid.[7]

In the presence of persistent endometrioma after 2 to 3 months at a transvaginal ultrasound scan, either cyst aspiration or administration of depot preparation of GnRH agonist or both cyst aspiration and depot preparation of GnRH agonist administration was done. The cyst aspiration was performed with USG guidance under general anesthesia. The diagnosis of chocolate cysts was confirmed by the aspiration of thick chocolate-colored fluid and then presence of hemosiderin laden macrophages with fibrosis at histopathology. Depot preparation of GnRH agonist was begun immediately after the cyst aspiration and continued for 3 months at four weekly interval. At the end of 4 weeks after the last injection, estradiol(E2) and progesterone(P4) levels were done, and only if E2 was less than 50 pg/ml and P4 was less than 2 ng/ml, the patient was taken up for *in vitro* fertilization or intracytoplasmic injection of sperm (IVF/ICSI). However, there were seven patients who underwent cyst aspiration but did not opt for GnRH analogs as a delay of 3 months was not feasible to them. There were three patients who had endometriomas lesser than 2 cm and had thickening and tenderness in both lateral fornices, so only GnRH analogs were administered without any cyst aspiration being performed, as they were diagnosed to be having severe endometriosis at laparoscopy but therapeutic fulguration of the endometriosis was not done at the time of diagnostic laparoscopy. These patients did not want a re-laparoscopy again with us and so to improve the outcome of IVF/ICSI they were given depot GnRH agonist preparation. The observations in each group, which included the number of days required for stimulation, total dose of stimulation required, number of oocytes obtained, quality of embryos and the pregnancy rates for each group were analyzed after tabulation and compared.

OBSERVATIONS AND RESULTS

Group B had 20 patients while group C and G had seven and three patients respectively. 50% of patients in group B, 86% of patients in group C and 67% of patients in group G were between 30 to 35 years of age. Only one patient in group B was more than 35 years old, viz. she was 39 years old (Table 1). 90% of

patients in group B, 57% of patients in group C and all patients in group G had primary infertility (Table 2). Majority of patients in all the three groups had one or two cysts (Fig. 1). Only 10% of patients in group B had four cysts and none of the patients had four cysts in groups C and G. All the patients in group G had one cyst less than 2 cm in size. 50% of patients in group B had cysts 2 to 3 cm in size and 43% of patients in group C had cysts more than 4 to 5 cm in size (Fig. 2). The most commonly associated factor in all the three groups was tubal, followed by uterine, male factor and PCO (Fig. 3). The mean duration of stimulation with gonadotrophins was 9 to 11 days (Fig. 4). The number of patients who required 9 to 11 days of stimulation showed a decreasing trend in groups B, G and C (Table 3). 80% of patients in group B, 66.6% of patients in group G and 57.1% in group C required 9 to 11 days of stimulation. Only 10% of patients in group B required more than 12 days of stimulation, while more than 25% of patients in both the groups C and G required more than 12 days (28.6% in group C and 33.3% in group G). The mean dose of gonadotrophins required in the groups B, G and C showed a progressively increasing trend (Table 4). 55% of patients in group B required less than 2500 IU while 33.3% of patients in group G and 28.6% in group C required less than 2500 IU of gonadotrophins (Table 5). In group B, 40% of the patients had a yield of 1 to 5 mature oocytes with a mean of 3.7 while 50% had 11 to 15 mature oocytes, and in 10% we obtained more than 16 but however less than 20 oocytes and none of them developed hyperstimulation. A progressive decrease was noted in the percentage of the number of cases with the optimum yield of 11 to 15 oocytes from group G to B and C, with the respective figures being 66.6, 28.6 and 50% for groups G, C and B. The addition of GnRH analog depot preparation was associated with an increase in the yield

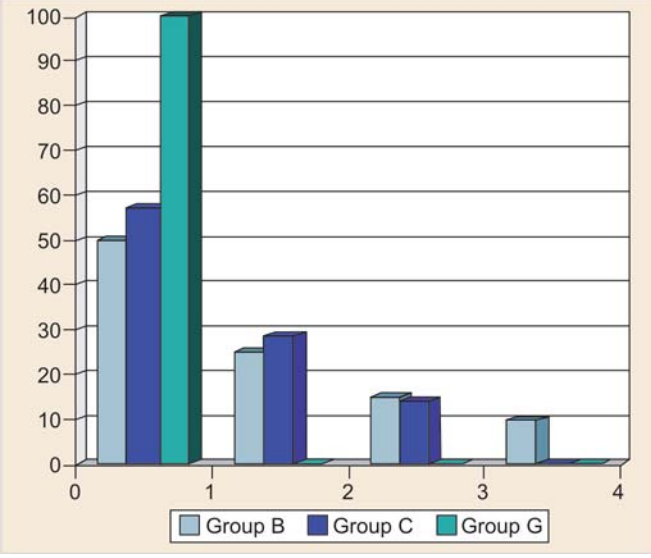

Fig. 1: Number of cysts

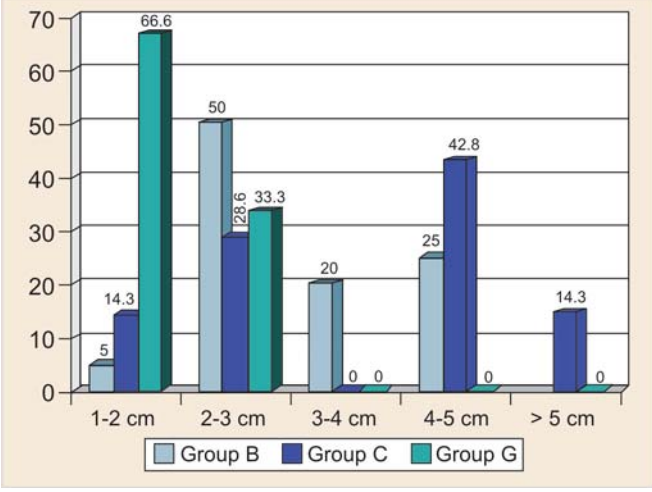

Fig. 2: Size of the cysts

Table 1: Age distribution

Age in years	Group B (n = 20)	%	Group C (n = 7)	%	Group G (n = 3)	%
20-25	2	10	0	0	0	0
25-30	7	35	1	14	1	33
30-35	10	50	6	86	2	67
> 35	1	5	0	0	0	0

Table 2: Type of infertility

Type of infertility	Group B (n = 20)	%	Group C (n = 7)	%	Group G (n = 3)	%
Primary	18	90	4	57	3	100
Secondary	2	10	3	43	0	0

Table 3: Duration of infertility

Duration in years	Group B (n = 20)	%	Group C (n = 7)	%	Group G (n = 3)	%
0-5	12	60	5	71.4	1	33.3
5-10	8	40	2	28.6	2	66.6

of mature oocytes (Fig 5). 40% in group B underwent ICSI and 60% IVF, of whom one patient required rescue ICSI. In groups C and G, 50% had IVF and the other 50% had ICSI. 85% of patients in group B, all patients in group G and 66.6% patients in group C had blastocysts transferred with a policy of not more than two blastocysts and not more than three embryos when a day 3 transfer was done. Prominent difference was observed between the clinical pregnancy rates in the three groups, with the maximum pregnancy rate in the group B, followed by group G and then C. The respective figures for the three groups B,G and C were 50, 42 and 33%. (Figs 6, 7 and 8). The p-value showed a trend, though not statistically significant, indicating the need for larger prospective studies with greater number of subjects (Table 6).

DISCUSSION

Ovarian endometriosis is known to be associated with infertility and pelvic pain. Differentiation of ovarian endometriotic cysts from cystic corpora lutea is clinically important because cystectomy for corpora lutea should be avoided in women with infertility, as it can be associated with the risk of postoperative adhesion formation and decreased ovarian reserve. Nieminen[8] suggested that free superficial implants undergo advanced secretory changes at the end of the menstrual cycle and show vascular necrosis and shedding at the time of menstruation. The small mucosal implants and congested vessels near the hilus of the ovary have been shown to be responsible for the bleeding in chocolate cysts. The treatment modality for endometriosis in patients with infertility could be either laparoscopic or open surgery. An alternative to surgery in some cases might be ultrasound-guided aspiration of ovarian endometriomas, a procedure first proposed by Aboulghar et al.[9] Whether it is just cyst aspiration or aspiration plus *in situ* irrigation or injection with a sclerosing agent in order to reduce recurrence, has no convincing published evidence. Sclerosing substances used vary from tetracycline[10] to methotrexate,[11] recombinant interleukin-2,[12] and/or ethanol.[13] For those patients who decline surgery, or in whom surgery is contraindicated, cyst aspiration may facilitate oocyte retrieval although the rates of recurrence are high. On the other hand, the expectant strategy is also associated with potential risks of:

Missing an occult early stage malignancy: Surgical removal and histological examination are considered mandatory to

Table 4: Type of FSH used

	Group B n = 20	Group C n = 7	Group G n = 3
150 IU HP urinary	18	7	3
Recombinant	2	0	0

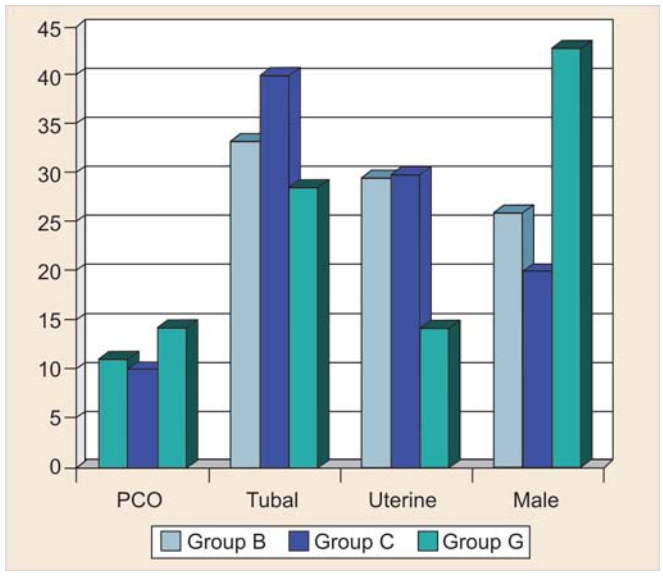

Fig. 3: Associated factors

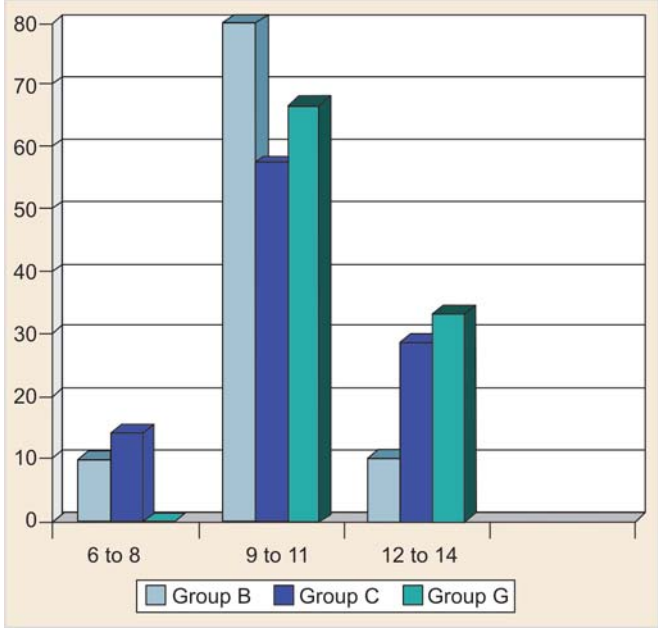

Fig. 4: Days of stimulation

Table 5: Mean dose of GT used

Mean dose of GT	Group B	%	Group C	%	Group G	%
1500-2000	5	25	–	14.3	0	0
2000-2500	6	30	–	14.3	1	33.3
2500-3000	1	5	2	28.6	1	33.3
3000-3500	5	25	2	28.6	0	0
3500-4000	3	15	0	0	1	33.3
> 4000	0	0	–	14.35	0	0

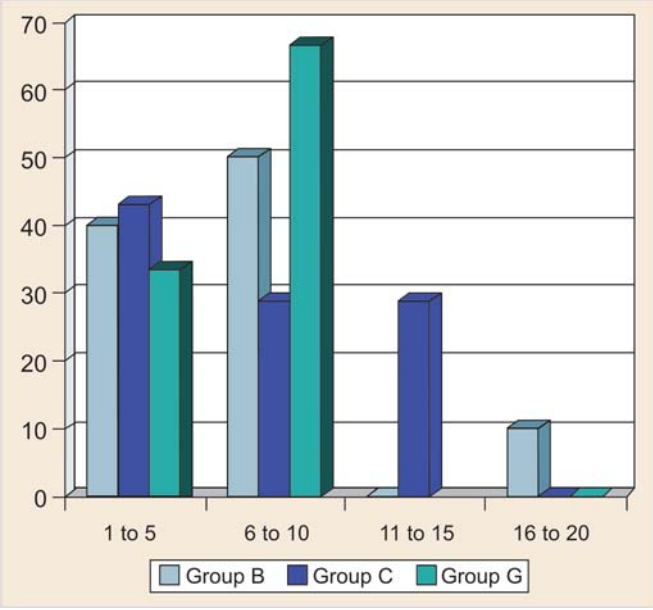

Fig. 5: Number of oocytes obtained

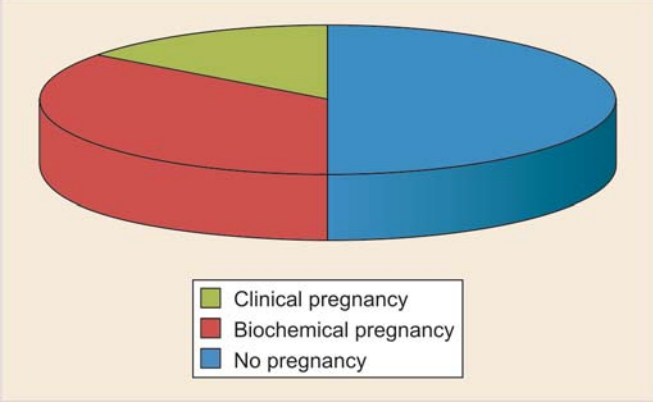

Fig. 6: Pregnancy rates for Group B

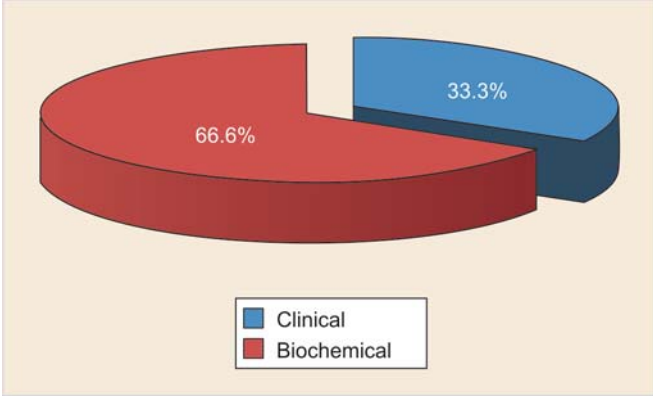

Fig. 7: Pregnancy rates for Group G

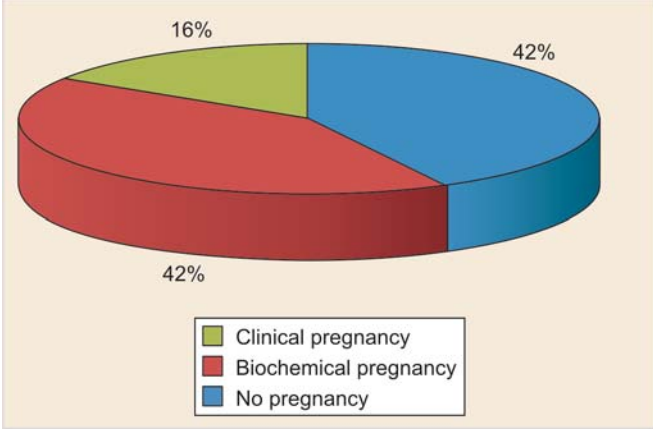

Fig. 8: Pregnancy rates for Group C

identify early ovarian cancer. Despite recent progresses in diagnostic tools,[14] this risk cannot currently be definitely ruled out. The two largest available series concerning the risk of occult malignancy in endometriotic samples reported a frequency of 0.8 and 0.9%, thus suggesting that this event is rare but possible.[15] A careful sonographic evaluation and strict monitoring over time may nearly annul this possibility.[16]

Development of a pelvic abscess: The bloody content of an endometrioma may serve as an excellent culture medium and may facilitate the spread of an infection process. Not surprisingly, the development of a pelvic abscess following oocyte retrieval has been repeatedly reported.[17] Clinical management of these cases is demanding and surgery may be necessary. The incidence of this frightful complication seems however rare. In an effort to determine the magnitude of this risk, Benaglia et al[18] have evaluated the frequency of this complication in women with endometriomas in a large consecutive series of 214 oocyte retrieval procedures. This complication was never observed (0.0%; 95% CI 0.0-1.7) suggesting that this risk is at least below 1.7%. In this regard, we however believe that prophylactic antibiotics should be routinely used and that every effort should be made to avoid the puncture of the endometrioma.

Progression of endometriosis: Since endometriosis is an estrogen-dependent disease and ART cycles determine a substantial increase in the peripheral levels of this hormone, a certain degree of alarmism about possible detrimental effects is common among affected patients and appears theoretically justified. Benaglia et al have recently reported reassuring data.[19] These authors have prospectively evaluated 48 women with endometriomas undergoing IVF and measured the dimension of the cysts before and 2 to 6 months after the procedure. They failed to document any significant modification.

Table 6: Pregnancy rates in different groups and their statistical significance

Outcome	Group B (%)	Group C (%)	Group G (%)	p-value
Clinical pregnancy	15	16	33.3	0.762
Biochemical pregnancy	35	42	66.6	0.725
No pregnancy	50	42	-	-

Other complications: Other complications of unoperated endometriomas include risk of causing the rupture of the endometrioma,[20] possible follicular fluid contamination with endometrioma content, difficulties during oocyte retrieval[21] and increased obstetric complications, such as preterm birth or intrauterine growth restriction.[22] Data regarding the first risk is anecdotal, whereas the effects of endometriotic fluid on the oocyte quality are still debated.[23] The benefits of surgery in facilitating oocyte retrieval may however be considered, taking into account endometrioma location within the ovary, specially if healthy follicles are located behind the cyst and the ovary is fixed. Finally, there is no evidence that surgery may significantly overcome the reported increased obstetric complications. In conclusion, what is the benefit, if any, of removing ovarian endometriotic cysts prior to IVF? There is convincing evidence that responsiveness to gonadotrophins after ovarian cystectomy is reduced and the number and quality of oocytes retrieved are at least not improved. Moreover, surgery exposes women to the dangerous risks of anesthesia and an operative procedure. In contrast, risks associated with expectant management are mostly anecdotal or of doubtful clinical relevance. Overall, laparoscopic surgical removal of ovarian endometriotic cysts prior to IVF does not offer any additional benefit in terms of fertility outcomes. We thus, generally recommend proceeding directly to IVF to reduce time to pregnancy, to avoid potential surgical complications and to limit patient costs. Surgery should be envisaged in specific circumstances, such as to treat concomitant pain symptoms which are refractory to medical treatments, or when malignancy cannot be reliably ruled out, or in the presence of large cysts. The diameter threshold for performing an operation before IVF should be adjusted according to the endometrioma location within the ovary. All decisions to operate a cyst beyond 3 or 4 cm are arbitrary, as there is no evidence to support one or the other. Surgeons should bear in mind that if all healthy growing follicles may be reached without damaging the endometrioma, cyst over 4 or even 5 cm do not require surgery in asymptomatic patients; however, smaller cysts that hide growing follicles, specially when the ovary is fixed, may require intervention.[24]

The effects of endometrioma on fertility outcomes with IVF and embryo transfer have been causally related to poor outcomes. The presence of endometriomas at the time of oocyte retrieval is associated with reduced number of retrieved oocytes, poorer quality of embryos and increased rates of early pregnancy losses.[25] The aspiration of endometrioma during oocyte retrieval is also associated with increased incidence of pelvic inflammatory disease.[26] A meta-analysis was done to evaluate the ovarian reserve and ovarian responsiveness to ovarian stimulation and assisted reproduction outcomes in patients with endometrioma. Decreased ovarian responsiveness to ovarian stimulation in patients with endometrioma may be due to a reduced number of follicles in these patients compared with controls ($p = 0.002$). The meta-analysis concluded that prospective randomized controlled trials are needed to assess whether surgical treatment versus no surgical treatment improves pregnancy outcomes in patients with endometrioma undergoing assisted reproduction cycles.[27]

Moreover, if a woman has undergone two or more laparoscopic surgeries for endometriosis and is for ART, but has recurrence of cysts which are > 5 cm, then it is better to subject the woman to cyst aspiration, which is a less invasive procedure as compared to laparoscopic surgery.

INTERNATIONAL GUIDELINES

The ESHRE (Kennedy et al 2005), the ASRM (The Practice Committee of the American Society for Reproductive Medicine, 2004) and RCOG (Royal College of Obstetricians and Gynaecologists 2006) have published guidelines and recommendations for the management of women with endometriosis. The three organizations recommend surgery for peritoneal endometriosis (stage I-II disease), although ESHRE and ASRM acknowledge that the benefit is limited. Consensus also exists on ovarian endometriomas (stage III-IV disease) as the effect of surgery is always defined 'positive'. There is a controversy even in the guidelines published. ESHRE and ASRM suggest surgical removal of endometriotic cysts, whereas the RCOG does not give a specific indication. Postoperative adjuvant treatment is consistently discouraged, as no evidence of its efficacy is available in terms of increased pregnancy rate. Surgery before IVF is suggested by ESHRE and RCOG only when an ovarian endometrioma of ≥ 4 cm in diameter is present, whereas ASRM does not recommend but emphasizes that the benefit of such a procedure is doubtful. It is important to remember that removal of cyst wall should not be excessive and the cauterization of the base of the cyst should be minimal to decrease the complication of reduced ovarian reserve. Recurrent endometriosis is addressed by ASRM, which suggests IVF in this group of patients instead of second surgery. The specific cases of rectovaginal lesions has not been dealt with by any of the organizations.[28]

Yap and colleagues searched the Cochrane Menstrual Disorders and Subfertility Group Trials Register (searched on 10 September, 2003), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 3 2003), MEDLINE (January 1966 to September 2003), EMBASE (January 1985 to September 2003) and reference lists of articles and also contacted researchers in the field. They studied the effectiveness of systemic medical therapies used for hormonal suppression before or after surgery for endometriosis, improvement of symptoms, pregnancy rates and overall tolerability. This meta-analysis showed insufficient evidence to use hormonal suppression in association with surgery for endometriosis for significant benefit with regard to any of the outcomes identified. There may be a benefit of improvement in AFS scores with the presurgical use of medical therapy. The possible benefit should be weighed in the context of the adverse effects and costs of these therapies.[29]

There are studies who quote a better success rate with IVF in the group of patients who have taken depot preparation of GnRH agonist for a total of 3 to 4 doses immediately prior to

ART. Data regarding adverse effects of this therapy on the mother or fetus are not available at present.

Casper et al have published that the use of GnRH agonist has a more favorable prognosis compared to antagonist with COH in patients with endometriosis. This is because GnRH agonist overcomes steroid dependent problems associated with endometriosis, improves follicular phase periovulatory defects and follicular luteinization, prevents premature LH surge, increases number of oocytes retrieved and improves fertilization with better pregnancy outcome.[30]

A Cochrane review has found that endometriosis patients who use gonadotropin-releasing hormone (GnRH) agonists in the run-up to IVF have improved outcomes. The live birth rate per woman was significantly higher in women with endometriosis who received gonadotropin-releasing hormone (GnRH) agonist for three to six months before commencing *in vitro* fertilization (IVF), compared to control groups. The number of women who became pregnant was also significantly higher. In a systematic review of the existing literature, reviewers, led by Professor Hassan Sallam, from Alexandria University in Egypt, found that giving GnRH agonists to women with endometriosis for 3 to 6 months before fertility treatment increased their chances of becoming pregnant more than four-fold. "The chances of having a live birth are also increased, though currently the data are not strong enough to show how great that increase is," said Sallam. Overall, the chances of pregnancy are lower in patients who have endometriosis than for those who have problems with their fallopian tubes. It has been thought that endometriosis may impair egg development and prevent the ovaries producing viable eggs, but Sallam says there are currently no data to show whether the treatment leads to better eggs or whether it facilitates implantation. In addition, there are no results to show whether one particular agonist is superior to the others, or whether the effects of therapy differ in women with mild or severe endometrial disease, the reviewers explain.[31] Several authors have concluded that extended pituitary down regulation prior to COH seems to be beneficial in stage III and IV endometriosis and this is attributable to the decrease in ectopic endometrial tissue in ovary, improved oocyte maturation and increased implantation rates.[32-34] As per Kostantinos et al, the use of gonadotropin-releasing hormone (GnRH) agonists in a long protocol appears to enhance the probability of conception in the presence of endometriosis. In addition, there is evidence to suggest that the use of prolonged down regulation with GnRH agonists prior to ovarian stimulation for *in vitro* fertilization (IVF) is beneficial for achieving pregnancy.[33] In a study by Oehninger et al *in vitro* fertilization (IVF) cycles were examined in patients with endometriosis who received gonadotropin-releasing hormone agonist (GnRHa) therapy in an effort to improve their response to stimulation. Twelve patients treated with an identical gonadotropin stimulation protocol, with and without GnRHa, were evaluated using paired analysis. In the GnRHa cycles, the total number of oocytes retrieved and transferred per cycle were higher than in the control cycles. In addition, use of the agonist lowered the cancellation rate from 33 to 0%, while a trend towards better pregnancy results was observed. When analyzed according to the stage of the disease, the patients with stage III or IV endometriosis had a more dramatic improvement with GnRHa. These data suggest that GnRHa therapy may be beneficial in some patients with endometriosis undergoing IVF. The results of this study are comparable with the results of the present study.[34] In the present study, in a small number of cases (30 cases), it was observed that the ultrasound-guided endometriotic cyst aspiration followed by the administration of GnRH analogs for three doses 4 weeks apart seemed better than administration of only GnRH analogs for 3 months or only cyst aspiration. If meta-analysis of several randomized controlled trials show a benefit of endometrioma aspiration and GnRH agonist depot administration, it will then become a norm in this group of patients who are undergoing ART, especially those who have recurrent endometriotic cysts. It is noteworthy that the ovarian responsiveness is damaged after the excision of ovarian endometriomas (Gupta et al 2006; Somigliana et al 2006a).[27,21] In a recent meta-analysis, Gupta et al showed that the number of developing follicles and the number of retrieved oocytes are lower in affected women when compared with controls who were unaffected. Data emerging from subsequent studies on this issue tend to confirm these findings (Esinler et al 2006; Somigliana et al 2006b; Yazbeck et al 2006; Cirpan et al 2007; Matalliotakis et al 2007; Kumbak et al 2008).[18] The harmful effect of endometriomas, and/or their excision, on ovarian responsiveness is further supported by studies focusing on women with monolateral disease and comparing responsiveness to hyperstimulation in the affected and in the contralateral intact gonad of the same patient (Ragni et al 2005; Somigliana et al 2006a; Duru et al 2007).[21] Collectively, these studies strongly support a marked reduction in the number of developing follicles and retrieved oocytes in the previously operated ovaries. Conversely, the potential impact of this endometrioma-related reduced responsiveness on the success rate of IVF is less recognized. In their meta-analysis, Gupta et al reported an OR for clinical pregnancy rate in women with the disease of 1.07 (95% CI 0.63–1.81) (Gupta et al 2006).[27] There are at least two main hypotheses to explain this contrasting result. Firstly, the damage could be quantitative rather than qualitative. In other words, in contrast to women whose ovarian reserve has naturally declined, fewer oocytes but of unaffected quality might be retrieved in affected women. Interestingly, in the single available prospective study comparing responsiveness of ovaries operated for endometriomas to contralateral intact gonads of the same patient, Ragni et al documented a marked reduction in the number of developing follicles and in the number of retrieved oocytes, but failed to observe differences in terms of fertilization rate between oocytes retrieved from affected and unaffected ovaries (Ragni et al 2005).[21] Secondly, ovarian endometriomas are mostly monolateral. Both gonads are involved only in 19 to 28% of cases (Somigliana et al 2008).[18] The contralateral intact ovary may adequately compensate for the reduced

function of the affected one. In this context, studies that have specifically focused on women with bilateral endometriomas should be considered more informative. Esinler et al compared 23 women with bilateral disease to 99 unaffected controls (Esinler et al 2006). In a larger study including 68 women operated on for bilateral endometriomas and 136 age-matched, unaffected controls, Somigliana et al showed a statistically significant reduction in the chances of success (Somigliana et al 2008).[18] The odds ratio (OR) for clinical pregnancy and delivery in the study group was 0.34 (95% CI 0.12-0.92) and 0.23 (95% CI 0.07-0.78) respectively. Collectively, insights emerging from these observational studies support the conclusion that ovarian responsiveness is modified in affected gonads. Although the injury could be more quantitative than qualitative, in some cases the insult can be so relevant that no or only few oocytes are retrieved. In this regard, it is noteworthy that Ragni et al documented a failure in the growth of codominant follicles in 34% of operated ovaries (Ragni et al 2005).[21] This issue may assume great relevance in women with bilateral disease. This could probably explain the greater duration of stimulation and reduced pregnancy rates in group C compared to group B or G. The message of the present article is to emphasize on cyst aspiration and pretreatment with GnRH analogs for patients with endometriomas prior to IVF/ICSI. This is because, when only cyst aspiration is performed without the back up of GnRH analogs, there are chances that the aspiration could be overdone with the aim of aspirating the cyst of its contents completely and eventually reduce the ovarian reserve.

CONCLUSION

Pretreating endometrioma by aspirating the cysts and administering three doses of GnRH analog depot preparation prior to IVF/ICSI seems to be better than administering GnRH analog depot preparation alone or aspirating the cysts alone in terms of the number of days required for stimulation, the number of oocytes obtained and the clinical pregnancy rates which had a statistically significant trend. However, a larger prospective cohort study might be required to ascertain the same in all cases of endometrioma who are going to be subjected to ART.

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