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SYMPOSIUM: REPRODUCTIVE SURGERY
REVIEW

Evidence-based management of endometrioma

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Abstract Endometrioma is commonly seen in women of reproductive age who may wish to preserve their ovarian function. Surgical treatment is associated with a high recurrence rate and its employment for women undergoing assisted conception has recently been challenged. Medical treatment has not been shown to be effective in controlling symptoms or improving fertility potential. The results of retrospective and non-randomized studies have been inconsistent and created an ongoing debate between gynaecologists and fertility specialists. This manuscript reviews and critically appraises the evidence for management of endometrioma in women of reproductive age. In asymptomatic women, surgical treatment is usually recommended for women above the age of 40 and for large endometriomas. Except for pelvic clearance, there is insufficient evidence to suggest that surgical treatment of endometrioma is better than medical treatment with respect to the long-term relief of symptoms and quality of life. Laparoscopic excision of ovarian endometrioma prior to IVF does not offer any additional benefit over expectant management. A large, well-designed, adequately powered randomized controlled study that compares the effects of surgical removal versus expectant management of endometrioma on ovarian performance and pregnancy outcomes in women undergoing IVF is warranted.

KEYWORDS: endometrioma, endometriosis, IVF, surgery

Introduction

Endometrioma is best defined as an ovarian pseudocyst arising from growth of ectopic endometrial tissue, which progressively invaginates the ovarian cortex (Hachisuga and Kawarabayashi, 2002). It is commonly seen in women of reproductive age who may complain of pelvic pain, dyspareunia and/or subfertility; some others may be asymptomatic. Around 17–44% of women with endometriosis also have endometriomas (Jenkins et al., 1986; Redwine, 1999). The incidence of endometriosis varies according to the population studied, with an average of 10–15% (Fauconnier and Chapron, 2005). Whereas detection of peritoneal endometriosis and adhesions typically requires laparoscopic assessment of the pelvis, endometriomas can be reliably diagnosed by transvaginal ultrasound scan (Eskenazi et al., 2001).

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Although there is some evidence to suggest that untreated endometriosis may resolve spontaneously in up to a third of women (Petta et al., 2005; Vercellini et al., 2003), the natural course of endometrioma is unknown. This is because of the lack of follow-up studies involving untreated women with endometrioma.

The pain-free interval and the quality of life are important key performance indicators of the treatment of endometriosis. As endometrioma is commonly associated with periovarian adhesions or deeply infiltrating endometriosis, it is not always possible to relate the woman's symptoms to the endometrioma *per se* (Fauconnier and Chapron, 2005). Surgical treatment of endometrioma is associated with a high recurrence rate (Busacca et al., 1999; Koga et al., 2006; Saleh and Tulandi, 1999) and its employment for women undergoing IVF has been recently challenged (Garcia-Velasco and Somigliana, 2009; Tsoumpou et al., 2009), though definite conclusions remain a matter of debate (Nama and Kalu, 2009). Endometriomas associated with severe endometriosis and multifocal disease (Chapron et al., 2009) require a multidisciplinary management approach. Surgery is usually recommended for large symptomatic endometriomas and for subfertile women (Jones and Sutton, 2003).

The results of retrospective and non-randomized studies have been inconsistent and created an ongoing debate between gynaecologists and fertility specialists. This manuscript reviews and critically appraises the evidence for management of endometrioma in women of reproductive age.

Materials and methods

MEDLINE, EMBASE and Cochrane library were searched from 1974 to February 2010 in full text for relevant publications. The search strategy used terms such as 'endometrioma', 'endometriosis', 'cystectomy', 'dysmenorrhoea', 'dyspareunia', 'pelvic pain', 'IVF', 'ICSI' and 'assisted conception'. The references of retrieved articles and relevant reviews were hand-searched to identify other potentially eligible studies missed by the initial search. Articles with inappropriate design were rejected from the review.

Management of endometrioma in subfertile women

The pathogenesis of infertility in women with endometriosis has not been clearly understood except in cases of distorted pelvic anatomy. Even in women undergoing IVF, pregnancy rates were found to be lower in patients with endometriosis compared with those with tubal factor infertility (Barnhart et al., 2002). The cumulative live birth rate after 1—4 cycles of IVF appears to be lower in stage III—IV endometriosis compared with stage I—II endometriosis or in women with tubal factor infertility (Kuivasaari et al., 2005).

Different causes have been postulated including impaired folliculogenesis, toxic effect of cytokines on oocyte or embryo quality and disordered fertilization and embryo implantation (Garcia-Velasco and Arici, 1999; Garrido et al., 2002; Harada et al., 2001; Jha et al., 1996; Pellicer et al., 1998). The effect of endometrioma *per se* on fertility has not been adequately investigated as it is rare to find isolated endometrioma without surrounding peritoneal disease. Indeed even minimal endometriosis is known to be associated with subfertility (Pritts and Taylor, 2003) and its treatment has been demonstrated to improve fertility outcome (Jacobson et al., 2003). Although there is some evidence to suggest disturbance of the physiological mechanisms leading to ovulation in ovaries with endometriomas (Benaglia et al., 2009; Kaplan et al., 1989), the exact causes are unknown. It may be speculated that the inflammatory reaction typically associated with the presence of endometriosis may play a role. Alternatively, the expanding ovarian cyst may cause pressure atrophy of the ovarian tissue or affect the normal vascularization of the ovary. Nakahara et al. (1998) found a higher incidence of apoptotic bodies in the ovarian membrana granulosa of patients with endometriosis than that of a control (male factor infertility) group. The incidence of apoptotic bodies correlated with the stage of endometriosis but was significantly higher in women with endometrioma, who in turn had lower numbers of developed follicles and retrieved oocytes after ovarian stimulation compared with the control group (Nakahara et al., 1998). It has also been suggested by some investigators that oocyte quality may be affected by ovarian endometriosis (Pal et al., 1998; Simón et al., 1994; Yanushpolsky et al., 1998).

Currently, there is insufficient data to clarify whether the endometrioma-related damage to ovarian reserve precedes or follows surgery. It has been shown that ovaries with endometriotic cysts already exhibited reduced number of follicles and vascular activity compared with other types of benign cysts (Maneschi et al., 1993). A retrospective analysis of 168 IVF cycles for normoresponder women with ovarian cysts (Kumbak et al., 2008) reported higher gonadotrophin consumption and lower oocyte yield in women with endometrioma compared with non-endometriotic simple cysts. Although the number of transferred grade-I embryos and the implantation rate were found to be higher in women with non-endometriotic cysts, there was no significant difference in pregnancy and ongoing pregnancy rates between the two groups.

Somigliana et al. (2006) evaluated 36 unoperated women with monolateral endometriomas who were selected for IVF. Significantly higher numbers of dominant follicles were seen in the unaffected gonads compared with the contralateral ones. This difference corresponded to a mean reduction of 25% (95% CI 6—44) in the affected ovaries. The deleterious effect was more evident in women with larger cysts, in those with more than one cyst and in those who were more responsive to ovarian stimulation (Somigliana et al., 2006). On the contrary, a small retrospective study (Wong et al., 2004) failed to show a significant difference in IVF pregnancy rate between women with untreated endometrioma and those who had peritoneal endometriosis without endometrioma.

Of note, the ovulation rate has been repeatedly shown to be reduced in ovaries operated on for endometrioma compared with contralateral intact ovaries (Candiani et al., 2005; Horikawa et al., 2008; Loh et al., 1999). There is insufficient evidence from randomized controlled trials (RCT) to support any treatment approach for subfertile women with endometrioma including those undergoing IVF.

Management of endometrioma prior to IVF

IVF is the mainstay of treatment for endometriosis-related subfertility (Kodama et al., 1996; Pal et al., 1998). Some gynaecologists would offer surgical removal of endometrioma prior to commencing ovarian stimulation for IVF. The effects of surgical removal of endometrioma on ovarian reserve and ovarian response to gonadotrophin stimulation have been the focus of much studies. A potential deleterious effect of surgery is the accidental removal or damage of normal ovarian tissue. Conservative laparoscopic surgery of ovarian cysts with well-defined ovarian capsules (e.g., teratomas and benign cystadenomas) rarely results in healthy ovarian tissue being removed (Hachisuga and Kawarabayashi, 2002; Muzii et al., 2002). Conversely, in more than 50% of the endometriomas removed, primordial follicles were seen histologically close to the cyst wall, probably due to the technical difficulties encountered in removing the cyst (Hachisuga and Kawarabayashi, 2002; Muzii et al., 2002). Stripping the endometriotic cyst wall is technically more difficult than non-endometriotic ovarian cysts, resulting in the inevitable removal of normal ovarian tissue (Exacoustos et al., 2004; Muzii et al., 2005; Tsolakidis et al., 2010). Drainage and coagulation of the cyst wall carries a risk of damage to the ovarian cortex. Both surgical techniques have been associated with reduced ovarian reserve and premature ovarian failure (Busacca et al., 2006; Horikawa et al., 2008). It has been reported that the risk of premature ovarian failure after laparoscopic removal of bilateral endometrioma is 2.4% (Busacca et al., 2006).

The treatment options for women with endometrioma who are about to undergo IVF treatment include surgery, expectant management and medical treatment. The results of studies that compared surgical treatment with no treatment of endometrioma were conflicting (Garcia-Velasco et al., 2004; Pabuccu et al., 2004; Suganuma et al., 2002; Tinkanen and Kujansuu, 2000; Wong et al., 2004). In addition, those studies were retrospective and included a small number of women. A systematic review and meta-analysis concluded that surgical treatment of endometrioma has no significant effect on IVF pregnancy rates and ovarian response to stimulation compared with no treatment (Tsoumpou et al., 2009).

The evidence from studies that have compared ovarian response in surgically removed endometrioma with the contralateral normal ovary is less convincing. Nevertheless, out of the six published studies (Duru et al., 2007; Ho et al., 2002; Loh et al., 1999; Ragni et al., 2005; Somigliana et al., 2003; Wyns and Donnez, 2003) all except one (Loh et al., 1999) showed a higher number of follicles whilst three studies (Ho et al., 2002; Ragni et al., 2005; Wyns and Donnez, 2003) reported a higher number of oocytes retrieved in the contralateral normal ovary compared with surgically removed endometrioma. Although the majority of the studies have suggested a negative effect of surgery on ovarian response to gonadotrophin stimulation, the retrospective nature and the small sample size lessen the conclusion of those studies. Only one RCT (Demirol et al., 2006) investigating the effect of surgical treatment of endometrioma on IVF outcome was found. The study showed some evidence of reduced ovarian response after surgical excision of endometrioma compared with drainage at the time of oocyte retrieval as evidenced by longer duration of stimulation, higher dose of gonadotrophins used, lower peak oestradiol concentrations and lower number of oocytes retrieved. Although the authors of this RCT did not find a difference in pregnancy rate between the two groups, they did not comment on the quality of the embryos and provided no data on the incidence of ovarian or pelvic infection.

In the absence of properly designed and powered RCT, the management of endometrioma prior to IVF remains controversial. Operating on an endometrioma >3 cm may interfere with follicle tracking and oocyte retrieval; nevertheless, some clinicians believe that excision of endometrioma prior to IVF improves ovarian response to gonadotrophin stimulation and live birth rates. The European Society of Human Reproduction and Embryology (ESHRE) recommend laparoscopic ovarian cystectomy if the endometrioma is ≥ 4 cm in diameter in order to confirm the diagnosis histologically, to reduce the risk of infection, to improve access to follicles and possibly to improve ovarian response. The authors advise that women should be counselled regarding the risks of reduced ovarian function after surgery and that the decision should be reconsidered if a woman has had previous ovarian surgery (Kennedy et al., 2005). An ESHRE-sponsored survey has been conducted (Gelbaya et al., 2010) to learn the strategies employed for the management of endometrioma (>3 cm) prior to IVF and to explore adherence to the ESHRE guidelines (Kennedy et al., 2005). An online questionnaire was sent to 396 members of the Special Interest Groups Reproductive Surgery and Endometriosis/Endometrium, with a response rate of 27%. Surgical management was the most common treatment (82.2%), with drainage and excision of the cyst wall being the preferred surgical approach (78.5%). The situation was different for women with previous ovarian surgery or recurrent endometrioma where surgical treatment was less commonly offered. It was reassuring that 47.7% of the responders offer expectant management of endometrioma before IVF in women with recurrent endometrioma or previous ovarian surgery.

Women with endometrioma may include women with normal or poor ovarian reserve. In women with normal response, it may be useful to use a prolonged down-regulation protocol based on the evidence that this protocol may improve pregnancy rates in women with endometriosis (Sallam et al., 2006).

Various treatment protocols have been devised to improve ovarian response and pregnancy outcome in women with predicted poor response to ovarian stimulation. Increasing the dose of gonadotrophins has not shown any benefit (Klinkert et al., 2005). There is insufficient evidence to support the routine use of the short gonadotrophin-releasing hormone (GnRH) agonist (co-flare) protocol in women with poor response (Shanbhag et al., 2007). A previous RCT comparing the GnRH antagonist with co-flare protocols in poor responders women reported significantly higher ongoing pregnancy rate in women who received flexible GnRH-antagonist protocol (Lainas et al., 2008). In this study, women who had previously had one or two failed IVF treatments in which five or less oocytes were retrieved

were included. In contrast, Pabuccu et al. (2007) recruited three different groups of patients: women with mild-to-moderate endometriosis ($n = 98$), those who had ovarian surgery for endometrioma ($n = 81$) and those with endometrioma and no history of previous surgery ($n = 67$). The subjects in each group were randomized to ovarian stimulation with either GnRH agonist or antagonist protocol for intracytoplasmic sperm injection (ICSI). Ovarian stimulation protocol did not affect the implantation or clinical pregnancy rates in women with mild to moderate endometriosis or women with unoperated endometrioma. With regard to women who had previous ovarian surgery for endometrioma implantation and clinical pregnancy rates were higher with the GnRH-agonist protocol than with the GnRH-antagonist protocol (22.6% and 39% versus 15.9% and 27.5%, respectively). Further studies are needed to determine the best protocol for ovarian stimulation in poor-responder women with endometrioma.

In summary, there is insufficient evidence to support routine surgical treatment of endometrioma in asymptomatic subfertile women. In line with the ESHRE guidelines, this review recommends expectant management if endometrioma is smaller than 4 cm and in cases of recurrent endometrioma. Women should be reassured that IVF does not influence the likelihood of endometriosis recurrence (Benaglia et al., 2010) or growth of endometrioma (Benaglia et al., 2009). Women who opt for surgical treatment of endometrioma prior to IVF should be offered ovarian reserve tests before surgery and those with reduced ovarian reserve should be discouraged from undergoing surgical treatment. Women undergoing ovarian surgery should be warned about the possible risk of surgery on ovarian function.

Management of endometrioma in women with pelvic pain

The relationship between chronic pelvic pain symptoms and endometrioma is not very clear. In studies using multivariate analysis, neither the presence of endometriomas nor any of their characteristics appears to correlate with painful symptoms (Chapron et al., 2003; Fauconnier et al., 2002; Koninckx et al., 1991; Porpora et al., 1999). In the majority of cases, it is not possible to relate the woman's symptoms to endometrioma *per se* but to the periovarian adhesions or deeply infiltrating endometriosis, which should be treated simultaneously (Fauconnier and Chapron, 2005).

Medical treatment is generally effective in relieving the endometriosis related pain. Hormonal compounds — combined oral contraceptives (COC), danazol, gestrinone, medroxyprogesterone acetate and GnRH agonist — have been found to be equally effective but the side-effect profiles vary (Davis et al., 2007; Prentice et al., 1999, 2000; Selak et al., 2007). The painful symptoms usually recur after discontinuation of medical treatment (Chapron et al., 2003). Several studies (Buttram et al., 1985; Donnez et al., 1990; Nisolle-Pochet et al., 1988; Rana et al., 1996) showed reduction in the size of small endometriomas after ovarian suppression with danazol or GnRH agonist but large endometriomas are not going to be completely resolved. The decrease in the size of endometrioma varied from 14% to 89% with a mean of 51% (Rana et al., 1996). As far as is known, there are no published studies investigating the effect of medical treatment, including hormonal suppression on pelvic pain in women with endometrioma. There is no reason why medical treatment cannot be offered to women with small symptomatic endometriomas, particularly for those women who wish to avoid surgery. In one study, hormonal suppression using GnRH agonist or danazol was found to be effective in reducing the size of endometrioma and in controlling pelvic pain and dysmenorrhoea (Rana et al., 1996). There is inconclusive evidence to show that non-steroidal anti-inflammatory drugs are effective in managing pain caused by endometriosis (Allen et al., 2009).

Surgical treatment of endometrioma is widely accepted as the first line management of symptomatic endometriomas, particularly for women who have completed their family (Jones et al., 2002). Surgical treatment include drainage with or without sclerotherapy, drainage with diathermy or laser vapourization of the cyst wall, drainage and stripping of the cyst wall (ovarian cystectomy) and radical treatment in the form of hysterectomy with or without oophorectomy. Uncontrolled studies reported significant relief of pain in a large proportion of cases after surgical treatment of endometrioma (Jones and Sutton, 2003; Sutton et al., 1997). Of note, the recurrence rate of symptomatic endometriosis after surgical treatment is consistently high (Fedele et al., 2006; Koga et al., 2006) and repeat surgery is not uncommon.

There is a significant risk of visceral injury as endometriomas are usually associated with severe peritoneal endometriosis and multifocal disease (Koninckx et al., 1996; Varol et al., 2003). Nevertheless, large endometriomas may be more susceptible to infection or rupture and should ideally be treated surgically.

Surgical treatment of endometrioma can be performed via laparotomy or laparoscopy, with no significant differences in the risk of recurrence of the cyst or pelvic pain symptoms and fertility outcome (Catalano et al., 1996; Milingos et al., 1999). It is recognized that laparotomy might be indicated in selected cases of severe endometriosis associated with dense extensive adhesions particularly in women who have had previous surgery. Recently, the authors of a UK survey on training in laparoscopic surgery found that 27% of trainees never performed a laparoscopy for the management of ectopic pregnancy and 52—62% never performed a laparoscopy for ovarian cyst or grade I—II endometriosis (Majmudar and Slack, 2009). Since surgery remains a widely used approach for treatment of endometrioma, bearing in mind the potential risk of iatrogenic premature ovarian failure, appropriate skills in laparoscopic surgery must constitute a core element of the subspecialty training in reproductive medicine.

Laparoscopic or transvaginal ultrasound guided drainage of endometrioma is associated with a high and rapid recurrence rate (Donnez et al., 1994; Troiano and Taylor, 1998; Vercellini et al., 1992; Zanetta et al., 1995) and is rarely effective in alleviating the patient's symptoms (Chan et al., 2003). It can be associated with a higher risk of pelvic infection (Muzii et al., 1995; Nargund and Parsons, 1995; Padilla, 1993; Yaron et al., 1994; Zanetta et al., 1995) and pelvic adhesions (Garvey et al., 1999; Muzii et al., 1995). Evidence from one RCT (Donnez et al., 1994) suggests that

the administration of GnRH agonist for 3 months after drainage of endometrioma may reduce the revised American Fertility Society grading score for endometriosis by 20% and the mean cyst diameter by 52%. The authors of this trial also reported histological evidence of decreased glandular and mitotic activity in women who received GnRH agonist for 3 months after drainage of the endometrioma. This approach may be useful in women who are at high risk of surgical complications such as those with a history of previous multiple surgery or those with frozen pelvis. This review advises prophylactic preoperative antibiotics before drainage of endometrioma to reduce the risk of infection.

Some investigators studied the effect of sclerotherapy on the recurrence of drained endometrioma by instillation of 95% ethanol (Hsieh et al., 2009; Noma and Yoshida, 2001; Yazbeck et al., 2009), 1–5% tetracycline (Aboulghar et al., 1993; Fisch and Sher, 2004), 600,000 IU interleukin-2 (Acién et al., 2003) or methotrexate (Mesogitis et al., 2000) into the cyst wall. The recurrence rate of endometrioma was lower with ethanol (13–15%) and methotrexate (18%) than after tetracycline (25%) or interleukin-2 (30%). Further studies evaluating the dose and efficacy of different sclerotherapeutic agents are warranted before this technique can be recommended for routine clinical practice.

Excision of endometrioma involves drainage followed by stripping of the cyst wall. Compared with drainage and coagulation, excision of endometrioma has the advantage of providing a tissue sample for histological diagnosis and exclusion of malignancy. In addition, the findings of two RCT (Alborzi et al., 2004; Beretta et al., 1998) and one Cochrane review (Hart et al., 2008) involving a total of 164 women with symptomatic endometrioma clearly indicate that excisional surgery offers advantage over drainage and ablation with respect to the recurrence of endometrioma and the symptoms of dysmenorrhoea, deep dyspareunia and non-menstrual pelvic pain. After excision of endometrioma, haemostasis can be achieved by bipolar or laser coagulation, intraovarian suturing or the use of fibrin glue to approximate the ovarian capsule and cover serosal defects. A small RCT (Pellicano et al., 2008) involving 32 women with single endometrioma undergoing ovarian cystectomy observed significantly lower rate of post-surgical ovarian adhesions in the group who had intraovarian sutures than in the group who had bipolar coagulation for haemostasis (30.8% versus 57.1%). In another prospective controlled non-randomized study involving 30 women with endometrioma (Takeuchi et al., 1996), the use of fibrin gel to approximate the ovarian capsule after surgical removal of endometrioma was associated with a significant decrease in the adhesion score. The decrease was most marked in women with endometriomas measuring 5 cm or more in diameter and for those with a high pre-operative adhesion score.

Excision of ovarian endometrioma is associated with a high recurrence rate. Busacca et al. (1999) prospectively evaluated 366 patients who underwent excision of endometrioma and followed them up for a minimum of 6 months post-operatively or 6 months after discontinuation of post-operative medical therapy. They observed a cumulative rate of ultrasonographic recurrence of 11.7% and a cumulative rate of a second surgery of 8.2% over 48 months. Ultrasonographic cyst recurrence was associated with pain recurrence in 73% of cases. Among the factors that were significantly associated with recurrence of endometrioma, the stage of the disease and a history of previous surgery for endometriosis were the most important. In another retrospective study involving 224 patients who were followed up for a minimum of 2 years after laparoscopic excision of endometrioma (Koga et al., 2006), the overall recurrence rate of endometrioma was 30.4%. A higher recurrence rate was observed in women who had received previous medical treatment for endometriosis and those with large endometrioma. In an attempt to compare the effect of primary versus repeat surgical treatment of endometrioma on the recurrence rate and ovarian function, Fedele et al. (2006) conducted a retrospective analysis of 305 primary surgeries and 54 reoperations for recurrent endometrioma in the same ovary as the primary cyst. The 5-year cumulative rates were not significantly different in both groups with respect to recurrence of endometrioma, retreatment requirement or pregnancy rate. However, women who had repeat surgery were more likely to need assisted conception and reported more irregular menstrual cycles associated with FSH concentrations $\geq$14 IU/ml.

There is not enough evidence to support the use of hormonal suppression prior to surgical treatment of endometriosis or endometrioma. One study comparing pre-surgical medical therapy with surgery alone showed a significant improvement in American Fertility Society scores in the medical therapy group but this may or may not be associated with better outcomes for the patients (Donnez et al., 1994). Although pre-operative hormonal therapy appears to reduce the size of endometrioma (Rana et al., 1996; Tsujioka et al., 2009), it may induce fibrosis of the capsule, thus increasing the difficulty in stripping the cyst wall without affecting the loss of ovarian follicles (Tsujioka et al., 2009).

A Cochrane systematic review involving 11 RCT concluded that there is insufficient evidence from the studies identified to conclude that hormonal suppression in association with surgery for endometriosis is associated with a significant benefit with regard to any of the outcomes identified (Yap et al., 2004). Jee et al. (2009) analysed the influence of post-operative GnRH-agonist treatment on disease recurrence after conservative laparoscopic surgery for ovarian endometriomas in 109 premenopausal women. The patients were divided into four treatment groups: expectant management (n = 37) and GnRH therapy for 3 (n = 28), 4 (n = 21) and 6 months (n = 23). The overall crude recurrence rate was 16.5% after follow-up for an average of 20 months. There was no significant difference in cumulative probabilities of disease recurrence at 24 and 36 months between the four groups. Similar findings were reported by Marana et al. (1994).

The evidence regarding the use of COC after surgical treatment of endometriosis or endometrioma is conflicting. Post-operative treatment with a COC has not been shown to be effective after surgical treatment of endometriosis (Muzii et al., 2000). With respect to endometrioma, a retrospective study involving 87 patients with endometrioma reported a lower recurrence rate in women who used the COC post-operatively (Takamura et al., 2009). The recurrence rate appeared to be related to the duration of COC use, being lower in women who continued the COC for 24

months than in women who discontinued the COC before the end of the study or those who never used the COC post-operatively. Similar findings from another retrospective study involving 277 patients with endometrioma were reported by Vercellini et al. (2008). In agreement with the aforementioned studies, a RCT (Seracchioli et al., 2010) of 239 women who underwent surgical excision of endometrioma reported a lower recurrence rate in women who used the COC either cyclically (14.7%) or continuously (8.2%) compared with non-users (29%). Two RCT (Muzii et al., 2000; Sesti et al., 2009) did not find a benefit from post-operative use of COC. The first RCT (Sesti et al., 2009) recruited 259 consecutive women who underwent laparoscopic unilateral/bilateral cystectomy for endometrioma. Patients were randomized to receive placebo ($n = 65$), GnRH agonist ($n = 65$), continuous low-dose monophasic oral contraceptives ($n = 64$) or dietary therapy (vitamins, mineral salts, lactic ferments, fish oil) ($n = 65$) for 6 months and were followed up for 18 months. There was no significant difference in the recurrence rate of endometrioma between women who received post-operative hormonal therapy (COC or GnRH agonist), dietary therapy or placebo. In the second RCT (Muzii et al., 2000) 70 patients were randomized to receive either low-dose cyclic COC post-operatively for 6 months or no treatment and were followed up for a mean duration of 22 months. The authors did not report a significant difference in the recurrence of endometrioma or moderate-to-severe pain or in the mean time to recurrence of symptoms or endometriomas between the study and the control group.

Hysterectomy with or without salpingo-oophorectomy may be justified in women with advanced endometriosis who do not wish to preserve their fertility. There are currently no RCT that have investigated the role of oophorectomy in management of advanced endometriosis. A retrospective study of 240 women with advanced endometriosis (Shakiba et al., 2008) reported that the lowest rates of re-operation for symptomatic endometriosis were in those women who had hysterectomy and bilateral oophorectomy as a primary procedure. In women who underwent local excision with ovarian preservation, the surgery-free percentages were 79.4%, 53.3% and 44.6% at 2, 5 and 7 years, respectively. In women who underwent hysterectomy with ovarian preservation, the 2-, 5- and 7-year re-operation-free percentages were 95.7%, 86.6% and 77.0%, respectively. In women who underwent hysterectomy without ovarian preservation, the percentages were 96.0%, 91.7% and 91.7%, respectively. In women between 30 and 39 years of age, removal of the ovaries did not significantly improve the surgery-free time. Since oophorectomy is associated with other significant disadvantages in terms of earlier menopause, the authors suggest that hysterectomy with ovarian conservation should be considered for advanced endometriosis in women younger than 40 years (Shakiba et al., 2008).

In another historical prospective study involving 138 women who had hysterectomy with or without ovarian tissue preservation for endometriosis (Namnoum et al., 1995), patients who had ovarian conservation had six times greater risk of developing recurrent pain and eight times greater risk of re-operation. It is quite possible that the risk of re-operation may increase in cases of endometrioma due to the high rate of cyst recurrence. In addition, the risk of ovarian cancer is slightly increased in women with endometrioma (Kobayashi et al., 2008). There is no consensus about how menopausal symptoms should be managed following oophorectomy for endometriosis. Oestrogen-only hormone therapy has been associated with disease recurrence. This has lead to recommendations to use tibolone or combined oestrogen and progestogen following oophorectomy for endometriosis in an attempt to prevent oestrogenic proliferation (Soliman and Hillard, 2006). However, there is some evidence that long-term combined hormone therapy may increase the risk of post-menopausal breast cancer compared with oestrogen alone, at least in older populations (Rossouw et al., 2002). Evidence for the risks associated with combined hormone therapy in younger women is limited. The absolute risk of morbidity in these younger women is believed to be lower and thus the benefit/risk ratio may be higher than in older women (MHRA, 2010).

In summary, treatment options for symptomatic endometrioma should take into account several factors including the woman's chronological age and her desire for fertility including any reproductive plans, previous surgery, concerns about increased risks of surgical complications or long term effects of medical therapy and the patient's preference. Medical treatment should be offered to symptomatic women with small endometrioma who wish to avoid surgery. Conservative surgical treatment is generally preferred for premenopausal women who wish to preserve their ovarian function. Excision of endometrioma offers advantage over drainage and ablation with respect to the recurrence of endometrioma and pelvic pain. Radical treatment is best reserved for older women who have completed their family.

Management of women with asymptomatic endometrioma

There is a wide variation in the reported incidence of endometriosis in asymptomatic women, ranging from 2% to 50% (Fauconnier and Chapron, 2005), while there is a lack of population-based studies reporting on the incidence of asymptomatic endometrioma in the general population. Although endometrioma is commonly associated with severe endometriosis (Chapron et al., 2009), there is no correlation between the stage of endometriosis and the severity of pelvic pain symptoms (Szendei et al., 2005). Management of asymptomatic endometrioma should take several factors into account including the accuracy of the diagnosis, the size of the cyst, the woman's age and her wish to preserve fertility and ovarian function. The local guidelines for management of suspected ovarian malignancy should be followed in cases of ovarian endometrioma. Ultrasound scanning and serum cancer antigen 125 (CA-125) may help to identify rare instances of ovarian cancer. However, CA-125 concentrations can be elevated in the presence of endometrioma (Kennedy et al., 2005). Due to the increased risk of ovarian cancer, surgical treatment is usually recommended for women above the age of 40 and for large endometriomas (Kobayashi et al., 2008). Expectant management is appropriate for younger women and for smaller endometriomas. It is prudent to follow-up women who opt for expectant management by annual ultrasound scan and serum CA-125.

Conclusions

Endometriomas are commonly seen in women of reproductive age who may wish to preserve their ovarian function and/or fertility. There is insufficient evidence to suggest that surgical treatment of endometrioma is better than medical treatment with respect to the long-term relief of symptoms and quality of life. Treatment of symptomatic women should be individualized according to the woman's age and her desire for fertility, previous surgery, long-term effects of medical therapy and the patient's preference. Although the evidence is insufficient, drainage and sclerotherapy of endometrioma, possibly followed by postoperative ovarian suppression for 3 months, may be valid for women with a history of previous multiple surgery or those with frozen pelvis who wish to preserve their ovaries. Laparoscopic excision of ovarian endometrioma prior to IVF does not offer any additional benefit over expectant management in terms of ovarian response to gonadotrophin stimulation or pregnancy outcome. A large, well-designed, adequately powered RCT that compares the effects of surgical removal versus expectant management of endometrioma on ovarian performance and pregnancy outcomes in women undergoing IVF is warranted. Until such a trial is conducted and definite conclusions can be drawn, the management of women with endometrioma prior to IVF should be individualized to maximize the chances of success and minimize the risks. All therapeutic options including conservative, medical or surgical treatment as well as the advantages and disadvantages should be fully discussed with the patient. Any decision for surgery should be carefully considered and balanced against the risks, especially in women who have had ovarian surgery or those with suboptimal ovarian reserve. If the patient opts for surgical treatment, she should be appropriately counselled about the potential risk of premature ovarian failure and the remote possibility of oophorectomy. Surgical treatment can be justified for women with concomitant pelvic pain not responding to medical treatment, when the cyst is larger than 4 cm or when malignancy cannot be reliably excluded.

References

Aboulghar, M.A., Mansour, R.T., Serour, G.I., Sattar, M., Ramzy, A.M., Amin, Y.M., 1993. Treatment of recurrent chocolate cysts by transvaginal aspiration and tetracycline sclerotherapy. J. Assist. Reprod. Genet. 10, 531—533.

Acién, P., Quereda, F.J., Gómez-Torres, M.J., Bermejo, R., Gutierrez, M., 2003. GnRH analogues, transvaginal ultrasound-guided drainage and intracystic injection of recombinant interleukin-2 in the treatment of endometriosis. Gynecol. Obstet. Invest. 55, 96—104.

Alborzi, S., Momtahan, M., Parsanezhad, M., Dehbashi, S., Zolghadri, J., Alborzi, S., 2004. A prospective, randomized study comparing laparoscopic ovarian cystectomy versus fenestration and coagulation in patients with endometriomas. Fertil. Steril. 82, 1633—1637.

Allen, C., Hopewell, S., Prentice, A., Gregory, D., 2009. Nonsteroidal anti-inflammatory drugs for pain in women with endometriosis. Cochrane Database Syst. Rev. 2, CD004753.

Barnhart, K., Dunsmoor-Su, R., Coutifaris, C., 2002. Effect of endometriosis on in vitro fertilization. Fertil. Steril. 77, 1148—1155.

Benaglia, L., Somigliana, E., Vighi, V., Nicolosi, A.E., Iemmello, R., Ragni, G., 2009. Is the dimension of ovarian endometriomas significantly modified by IVF—ICSI cycles? Reprod. Biomed. Online 18, 401—406.

Benaglia, L., Somigliana, E., Vercellini, P., Benedetti, F., Iemmello, R., Vighi, V., 2010. The impact of IVF procedures on endometriosis recurrence. Eur. J. Obstet. Gynecol. Reprod. Biol. 148, 49—52.

Beretta, P., Franchi, M., Ghezzi, F., Busacca, M., Zupi, E., Bolis, P., 1998. Randomized clinical trial of two laparoscopic treatments of endometriomas: cystectomy versus drainage and coagulation. Fertil. Steril. 70, 1176—1180.

Busacca, M., Marana, R., Caruana, P., Candiani, M., Muzii, L., Calia, C., 1999. Recurrence of ovarian endometrioma after laparoscopic excision. Am. J. Obstet. Gynecol. 180, 519—523.

Busacca, M., Riparini, J., Somigliana, E., Oggioni, G., Izzo, S., Vignali, M., Candiani, M., 2006. Postsurgical ovarian failure after laparoscopic excision of bilateral endometriomas. Am. J. Obstet. Gynecol. 195, 421—425.

Buttram Jr., V.C., Reiter, R.C., Ward, S., 1985. Treatment of endometriosis with danazol: report of a 6 year prospective study. Fertil. Steril. 43, 353—357.

Candiani, M., Barbieri, M., Bottani, B., Bertulessi, C ., Vignali, M., Agnoli, B., Somigliana, E., Busacca, M., 2005. Ovarian recovery after laparoscopic enucleation of ovarian cysts: insights from echographic short-term postsurgical follow-up. J. Minim. Invasive. Gynecol. 12, 409—414.

Catalano, G.F., Marana, R., Caruana, P., Muzii, L., Mancuso, S., 1996. Laparoscopy versus microsurgery by laparotomy for excision of ovarian cysts in patients with moderate or severe endometriosis. J. Am. Assoc. Gynecol. Laparosc. 3, 267—270.

Chan, L.Y., So, W.W., Lao, T.T., 2003. Rapid recurrence of endometrioma after transvaginal ultrasound-guided aspiration. Eur. J. Obstet. Gynecol. Reprod. Biol. 15, 196—198.

Chapron, C., Fauconnier, A., Dubuisson, J.B., Barakat, H., Vieira, M., Breart, G., 2003. Deep infiltrating endometriosis: relation between severity of dysmenorrhoea and extent of disease. Hum. Reprod. 18, 760—766.

Chapron, C., Pietin-Vialle, C., Borghese, B., Davy, C., Foulot, H., Chopin, N., 2009. Associated ovarian endometrioma is a marker for greater severity of deeply infiltrating endometriosis. Fertil. Steril. 92, 453—457.

Davis, L.J., Kennedy, S.S., Moore, J., Prentice, A., 2007. Oral contraceptives for pain associated with endometriosis. Cochrane Database Syst. Rev. 3, CD001019.

Demirol, A., Guven, S., Baykal, C., Gurgan, T., 2006. Effect of endometrioma cystectomy on IVF outcome: a prospective randomized study. Reprod. Biomed. Online 12, 639—643.

Donnez, J., Nisolle, M., Casanas-Roux, F., 1990. Endometriosis-associated infertility: evaluation of preoperative use of danazol, gestrinone and buserelin. Int. J. Fertil. 35, 297—301.

Donnez, J., Nisolle, M., Gillerot, S., Anaf, V., Clerckx-Braun, F., Casanas-Roux, F., 1994. Ovarian endometrial cysts: the role of gonadotropin-releasing hormone agonist and/or drainage. Fertil. Steril. 62, 63—66.

Duru, N.K., Dede, M., Acikel, C.H., Keskin, U., Fidan, U., Baser, I., 2007. Outcome of in vitro fertilization and ovarian response after endometrioma stripping at laparoscopy and laparotomy. J. Reprod. Med. 52, 805—809.

Eskenazi, B., Warner, M., Bonsignore, L., Olive, D., Samuels, S., Vercellini, P., 2001. Validation study of nonsurgical diagnosis of endometriosis. Fertil. Steril. 76, 929—935.

Exacoustos, C., Zupi, E., Amadio, A., Szabolcs, B., De Vivo, B., Marconi, D., Elisabetta Romanini, M., Arduini, D., 2004. Laparoscopic removal of endometriomas: sonographic evaluation of residual functioning ovarian tissue. Am. J. Obstet. Gynecol. 191, 68—72.

Fauconnier, A., Chapron, C., Dubuisson, J.B., Vieira, M., Dousset, B., Breart, G., 2002. Relation between pain symptoms and the anatomic location of deep infiltrating endometriosis. Fertil. Steril. 78, 719–726.

Fauconnier, A., Chapron, C., 2005. Endometriosis and pelvic pain: epidemiological evidence of the relationship and implications. Hum. Reprod. Update 11, 595–606.

Fedele, L., Bianchi, S., Zanconato, G., Berlanda, N., Raffaelli, R., Fontana, E., 2006. Laparoscopic excision of recurrent endometriomas: long-term outcome and comparison with primary surgery. Fertil. Steril. 85, 694–699.

Fisch, J.D., Sher, G., 2004. Sclerotherapy with 5% tetracycline is a simple alternative to potentially complex surgical treatment of ovarian endometriomas before in vitro fertilization. Fertil. Steril. 82, 437–441.

Garcia-Velasco, J.A., Arici, A., 1999. Is the endometrium or oocyte/embryo affected in endometriosis? Hum. Reprod. 14 (Suppl. 2), 77–89.

Garcia-Velasco, J.A., Mahutte, N.G., Corona, J., Zuniga, V., Giles, J., Arici, A., Pellicer, A., 2004. Removal of endometriomas before in vitro fertilization does not improve fertility outcomes: a matched, case-control study. Fertil. Steril. 81, 1194–1197.

Garcia-Velasco, J.A., Somigliana, E., 2009. Management of endometriomas in women requiring IVF: to touch or not to touch. Hum. Reprod. 24, 496–501.

Garrido, N., Navarro, J., García-Velasco, J., Remoh, J., Pellice, A., Simón, C., 2002. The endometrium versus embryonic quality in endometriosis-related infertility. Hum. Reprod. Update 8, 95–103.

Garvey, T.S., Kazer, R.R., Milad, M.P., 1999. Severe pelvic adhesions following attempted ultrasound-guided drainage of bilateral ovarian endometriomas. Hum. Reprod. 14, 2748–2750.

Gelbaya, T.A., Gordts, S., D'Hooghe, T.M., Gergolet, M., Nardo, L.G., 2010. Management of endometrioma prior to in vitro fertilization: compliance with ESHRE guidelines. Reprod. Biomed. Online (Ahead of publication).

Hachisuga, T., Kawarabayashi, T., 2002. Histopathological analysis of laparoscopically treated ovarian endometriotic cysts with special reference to loss of follicles. Hum. Reprod. 17, 432–435.

Harada, T., Iwabe, T., Terakawa, N., 2001. Role of cytokines in endometriosis. Fertil. Steril. 76, 1–10.

Hart, R.J., Hickey, M., Maouris, P., Buckett, W., Garry, R., 2008. Excisional surgery versus ablative surgery for ovarian endometriomata. Cochrane Database Syst. Rev. 2, CD004992.

Ho, H.Y., Lee, R.K., Hwu, Y.M., Lin, M.H., Su, J.T., Tsai, Y.C., 2002. Poor response of ovaries with endometrioma previously treated with cystectomy to controlled ovarian hyperstimulation. J. Assist. Reprod. Genet. 19, 507–511.

Horikawa, T., Nakagawa, K., Ohgi, S., Kojima, R., Nakashima, A., Ito, M., Takahashi, Y., Saito, H., 2008. The frequency of ovulation from the affected ovary decreases following laparoscopic cystectomy in infertile women with unilateral endometrioma during a natural cycle. J. Assist. Reprod. Genet. 25, 239–244.

Hsieh, C.L., Shiau, C.S., Lo, L.M., Hsieh, T.T., Chang, M.Y., 2009. Effectiveness of ultrasound-guided aspiration and sclerotherapy with 95% ethanol for treatment of recurrent ovarian endometriomas. Fertil. Steril. 91, 2709–2713.

Jacobson, T.Z., Barlow, D.H., Koninckx, P.R., Olive, D., Farquhar, C., 2003. Laparoscopic surgery for subfertility associated with endometriosis. Cochrane Database Syst. Rev. 4, CD001398.

Jee, B.C., Lee, J.Y., Suh, C.S., Kim, S.H., Choi, Y.M., Moon, S.Y., 2009. Impact of GnRH agonist treatment on recurrence of ovarian endometriomas after conservative laparoscopic surgery. Fertil. Steril. 91, 40–45.

Jenkins, S., Olive, D.L., Haney, A.F., 1986. Endometriosis: pathogenetic implications of the anatomic distribution. Obstet. Gynecol. 67, 335–338.

Jha, P., Farooq, A., Agrawal, N., Buckshee, K., 1996. In vitro sperm phagocytosis by human peritoneal macrophage in endometriosis-associated infertility. Am. J. Reprod. Immunol. 36, 235–237.

Jones, K.D., Fan, A., Sutton, C.J.G., 2002. The ovarian endometrioma: why is it so poorly managed? Indicators from anonymous survey. Hum. Reprod. 17, 845–849.

Jones, K.D., Sutton, C., 2003. Patient satisfaction and changes in pain scores after ablative laparoscopic surgery for stage III–IV endometriosis and endometriotic cysts. Fertil. Steril. 79, 1086–1090.

Kaplan, C.R., Eddy, C.A., Olive, D.L., Schenken, R.S., 1989. Effect of ovarian endometriosis on ovulation in rabbits. Am. J. Obstet. Gynecol. 160, 40–44.

Kennedy, S., Bergqvist, A., Chapron, C., D'Hooghe, T., Dunselman, G ., Greb, R., Hummelshoj, L., Prentice, A., Saridogan, E., 2005. ESHREguideline for the diagnosis and treatment of endometriosis. Hum. Reprod. 20, 2698–2704.

Klinkert, E.R., Broekmans, F.J.M., Looman, C.W.N., Habbema, J.D.F., te Velde, E.R., 2005. Expected poor responders on the basis of an antral follicle count do not benefit from a higher starting dose of gonadotrophins in IVF treatment: a randomized controlled trial. Hum. Reprod. 20, 611–615.

Kobayashi, H., Sumimoto, K., Kitanaka, T., Yamada, Y., Sado, T., Sakata, M., Yoshida, S., Kawaguchi, R., Kanayama, S., Shigetomi, H., Haruta, S., Tsuji, Y., Ueda, S., Terao, T., 2008. Ovarian endometrioma - risks factors of ovarian cancer development. Eur. J. Obstet. Gynecol. Reprod. Biol. 138, 187–193.

Kodama, H., Fukuda, J., Karube, H., Matsui, T., Shimizu, Y., Tanaka, T., 1996. Benefit of in vitro fertilization treatment of endometriosis associated infertility. Fertil. Steril. 66, 974–979.

Koga, K., Takemura, Y., Osuga, Y., Yoshino, O., Hirota, Y., Hirata, T., Morimoto, C., Harada, M., Yano, T., Taketani, Y., 2006. Recurrence of ovarian endometrioma after laparoscopic excision. Hum. Reprod. 21, 2171–2174.

Koninckx, P.R., Meuleman, C., Demeyere, S., Lesaffre, E., Cornillie, F.J., 1991. Suggestive evidence that pelvic endometriosis is a progressive disease, whereas deeply infiltrating endometriosis is associated with pelvic pain. Fertil. Steril. 55, 759–765.

Koninckx, P.R., Timmermans, B., Meuleman, C., Penninckx, F., 1996. Complications of CO_2-laser endoscopic excision of deep endometriosis. Hum. Reprod. 11, 2263–2268.

Kuivasaari, P., Hippeläinen, M., Anttila, M., Heinonen, S., 2005. Effect of endometriosis on IVF/ICSI outcome: stage III/IV endometriosis worsens cumulative pregnancy and live-born rates. Hum. Reprod. 20, 3130–3135.

Kumbak, B., Kahraman, S., Karlikaya, G., Lacin, S., Guney, A., 2008. In vitro fertilization in normoresponder patients with endometriomas: comparison with basal simple ovarian cysts. Gynecol. Obstet. Invest. 65, 212–216.

Lainas, T.G., Sfontouris, I.A., Papanikolaou, E.G., Zorzovilas, J.Z., Petsas, G.K., Lainas, G.T., Kolibianakis, E.M., 2008. Flexible GnRH antagonist versus flare-up GnRH agonist protocol in poor responders treated by IVF: a randomized controlled trial. Hum. Reprod. 23, 1355–1358.

Loh, F.H., Tan, A.T., Kumar, J., Ng, S.C., 1999. Ovarian response after laparoscopic ovarian cystectomy for endometriotic cysts in132 monitored cycles. Fertil. Steril. 72, 316–321.

Majmudar, T., Slack, M., 2009. Laparoscopy training for obstetrics and gynaecology trainees? A pilot study in the Easter Deanery, UK. Gynecol. Surg. 6, 45–50.

Maneschi, F., Marasa, L., Incadela, S., Mazzarese, M., Zupi, E., 1993. Ovarian cortex surrounding benign neoplasms: a histologic study. Am. J. Obstet. Gynecol. 169, 388–393.

Marana, R., Costantini, W., Muzii, L., Uglietti, A., Caruana, P., Arnold, M., 1994. Laparoscopic excision of ovarian endometriomas: does post-operative medical treatment prevent recurrence? J. Am. Assoc. Gynecol. Laparosc. 4 (Pt. 2), S20.

Mesogitis, S., Antsaklis, A., Daskalakis, G., Papantoniou, N., Michalas, S., 2000. Combined ultrasonographically guided drainage and methotrexate administration for treatment of endometriotic cysts. Lancet 355, 1160.

MHRA [Internet]. Hormone Replacement Therapy: Update Advice. Drug Safety Update, 2007 September; 1 (2). <http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON2032234/> (cited 01.18.10).

Milingos, S., Loutradis, D., Kallipolitis, G., l., Liapi, A., Drakakis, P., Antsaklis, A., Michalas, S., 1999. Comparison of laparoscopy with laparotomy for the treatment of extensive endometriosis with large endometriomata. J. Gynecol. Surg. 15, 131–136.

Muzii, L., Marana, R., Caruana, P., Catalano, G.F., Mancuso, S., 1995. Laparoscopic findings after transvaginal ultrasound-guided aspiration of ovarian endometriomas. Hum. Reprod. 10, 2902–2903.

Muzii, L., Bianchi, A., Crocè, C., Manci, N., Panici, P.B., 2002. Laparoscopic excision of ovarian cysts: is the stripping technique a tissue-sparing procedure? Fertil. Steril. 77, 609–614.

Muzii, L., Bellati, F., Bianchi, A., Palaia, I., Manci, N., Zullo, M.A., Angioli, R., Panici, P.B., 2005. Laparoscopic stripping of endometriomas: a randomized trial on different surgical techniques: Part II. Pathological results. Hum. Reprod. 20, 1987–1992.

Muzii, L., Marana, R., Caruana, P., Catalano, G.F., Margutti, F., Panici, P.B., 2000. Postoperative administration of monophasic combined oral contraceptives after laparoscopic treatment of ovarian endometriomas: a prospective, randomized trial. Am. J. Obstet. Gynecol. 183, 588–592.

Nakahara, K., Saito, H., Saito, T., Ito, M., Ohta, M., Takahasi, T., Hiroi, M., 1998. Ovarian fecundity in patients with endometriosis can be estimated by the incidence of apoptotic bodies. Fertil. Steril. 69, 931–935.

Nama, V., Kalu, E., 2009. Management of endometrioma in women embarking on IVF: paucity of good quality evidence. Fertil. Steril. 92, e63.

Namnoum, A.B., Hickman, T.N., Goodman, S.B., Gehlbach, D.L., Rock, J.A., 1995. Incidence of symptom recurrence after hysterectomy for endometriosis. Fertil. Steril. 64, 898–902.

Nargund, G., Parsons, J., 1995. Infected endometriotic cysts secondary to oocyte aspiration for in-vitro fertilization. Hum. Reprod. 10, 1555.

Nisolle-Pochet, M., Casanas-Roux, F., Donnez, J., 1988. Histologic study of ovarian endometriosis after hormonal therapy. Fertil. Steril. 49, 423–426.

Noma, J., Yoshida, N., 2001. Efficacy of ethanol sclerotherapy for ovarian endometriomas. Int. J. Gynecol. Obstet. 72, 35–39.

Pabuccu, R., Onalan, G., Goktolga, U., Kucuk, T., Orhon, E., Ceyhan, T., 2004. Aspiration of ovarian endometriomas before intracytoplasmic sperm injection. Fertil. Steril. 82, 705–711.

Pabuccu, R., Onalan, G., Kaya, C., 2007. GnRH agonist and antagonist protocols for stage I–II endometriosis and endometrioma in in vitro fertilization/intracytoplasmic sperm injection cycles. Fertil. Steril. 88, 832–839.

Padilla, S.L., 1993. Ovarian abscess following puncture of an endometrioma during ultrasound-guided oocyte retrieval. Hum. Reprod. 8, 1282–1283.

Pal, L., Shrifren, J.L., Isaacson, K.B., Chang, Y., Leykin, L., Toth, T.L., 1998. Impact of varying stages of endometriosis on the outcome of in vitro fertilization–embryo transfer. J. Assist. Reprod. Genet. 15, 27–31.

Pellicano, M., Bramante, S., Guida, M., Bifulco, G., Di Spiezio Sardo, A., Cirillo, D., Nappi, C., 2008. Ovarian endometrioma: postoperative adhesions following bipolar coagulation and suture. Fertil. Steril. 89, 796–799.

Pellicer, A., Valbuena, D., Bauset, C., Albert, C., Bonilla- Musoles, F., Remohi, J., Simon, C., 1998. The follicular endocrine environment in stimulated cycles of women with endometriosis: steroid levels and embryo quality. Fertil. Steril. 69, 1135–1141.

Petta, C.A., Ferriani, R.A., Abrao, M.S., Hassan, D., Rosa, E., Silva, J.C., Podgaec, S., Bahamondes, L., 2005. Randomized clinical trial of a levonorgestrel-releasing intrauterine system and a depot GnRH analogue for the treatment of chronic pelvic pain in women with endometriosis. Hum. Reprod. 20, 1993–1998.

Porpora, M.G., Koninckx, P.R., Piazze, J., Natili, M., Colagrande, S., Cosmi, E.V., 1999. Correlation between endometriosis and pelvic pain. J. Am. Assoc. Gynecol. Laparosc. 6, 429–434.

Prentice, A., Deary, A., Goldbeck-Wood, S., Farquhar, C., Smith, S., 1999. Gonadotrophin-releasing hormone analogues for pain associated with endometriosis. Cochrane Database Syst. Rev. 2, CD000346.

Prentice, A., Deary, A.J., Bland, E., 2000. Progestagens and anti-progestagens for pain associated with endometriosis. Cochrane Database Syst. Rev. 2, CD002122.

Pritts, E.A., Taylor, R.N., 2003. An evidence-based evaluation of endometriosis-associated infertility. Endocrinol. Metab. Clin. North Am. 32, 653–667.

Ragni, G., Somigliana, E., Benedetti, F., Paffoni, A., Vegetti, W., Restelli, L., Crosignani, P.G., 2005. Damage to ovarian reserve associated with laparoscopic excision of endometriomas: a quantitative rather than a qualitative injury. Am. J. Obstet. Gynecol. 193, 1908–1914.

Rana, N., Thomas, S., Rotman, C., Dmowski, W.P., 1996. Decrease in the size of ovarian endometriomas during ovarian suppression in stage IV endometriosis. Role of preoperative medical treatment. J. Reprod. Med. 41, 384–392.

Redwine, D.B., 1999. Ovarian endometriosis: a marker for more extensive pelvic and intestinal disease. Fertil. Steril. 72, 310–315.

Rossouw, J.E., Anderson, G.L., Prentice, R.L., La Croix, A.Z., Kooperberg, C., Stefanick, M.L., Jackson, R.D., Beresford, S.A., Howard, B.V., Johnson, K.C., Kotchen, J.M., Ockene, J., 2002. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 288, 321–333.

Saleh, A., Tulandi, T., 1999. Reoperation after laparoscopic treatment of ovarian endometriomas by excision and by fenestration. Fertil. Steril. 72, 322–324.

Sallam, H.N., Garcia-Velasco, J.A., Dias, S., Arici, A., 2006. Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis. Cochrane Database Syst. Rev. 25, CD004635.

Selak, V., Farquhar, C., Prentice, A., Singla, A., 2007. Danazol for pelvic pain associated with endometriosis. Cochrane Database Syst. Rev. 4, CD000068.

Seracchioli, R., Mabrouk, M., Frasca, C., Manuzzi, L., Montanari, G., Keramyda, A., Venturoli, S., 2010. Long-term cyclic and continuous oral contraceptive therapy and endometrioma recurrence: a randomized controlled trial. Fertil. Steril. 93, 52–56.

Sesti, F., Capozzolo, T., Pietropolli, A., Marziali, M., Bollea, M.R., Piccione, E., 2009. Recurrence rate of endometrioma after laparoscopic cystectomy: a comparative randomized trial between post-operative hormonal suppression treatment or dietary therapy vs. placebo. Eur. J. Obstet. Gynecol. Reprod. Biol. 147, 72–77.

Shakiba, K., Bena, J.F., McGill, K.M., Minger, J., Falcone, T., 2008. Surgical treatment of endometriosis: a 7-year follow-up on the requirement for further surgery. Obstet. Gynecol. 111, 1285–1292.

Shanbhag, S., Aucott, L., Bhattacharya, S., Hamilton, M.A., McTavish, A.R., 2007. Intervention for poor responders to controlled ovarian hyperstimulation in IVF. Cochrane Database Syst. Rev. 1, CD004379.

Simon, C., Gutierrez, A., Vidal, A., de los Santos, M.J., Tarrin, J.J., Remohi, J., Pellicer, A., 1994. Outcome of patients with endometriosis in assisted reproduction: results from in-vitro fertilization and oocyte donation. Hum. Reprod. 9, 725—729.

Soliman, N.F., Hillard, T.C., 2006. Hormone replacement therapy in women with past history of endometriosis. Climacteric 9, 325—335.

Somigliana, E., Ragni, G., Benedetti, F., Borroni, R., Vegetti, W., Crosignani, P.G., 2003. Does laparoscopic excision of endometriotic ovarian cysts significantly affect ovarian reserve? Insights from IVF cycles. Hum. Reprod. 18, 2450—2453.

Somigliana, E., Infantino, M., Benedetti, F., Arnoldi, M., Calanna, G., Ragni, G., 2006. The presence of ovarian endometriomas is associated with a reduced responsiveness to gonadotropins. Fertil. Steril. 86, 192—196.

Suganuma, N., Wakahara, Y., Ishida, D., Asano, M., Kitagawa, T., Katsumata, Y., Moriwaki, T., Furuhashi, M., 2002. Pretreatment for ovarian endometrial cyst before in vitro fertilization. Gynecol. Obstet. Invest. 54 (Suppl. 1), 36—42.

Sutton, C.J., Ewen, S.P., Jacobs, S.A., Whitelaw, N.L., 1997. Laser laparoscopic surgery in the treatment of ovarian endometriomas. J. Am. Assoc. Gynecol. Laparosc. 4, 319—323.

Szendei, G., Hernádi, Z., Dévényi, N., Csapó, Z., 2005. Is there any correlation between stages of endometriosis and severity of chronic pelvic pain? Possibilities of treatment. Gynecol. Endocrinol. 21, 93—100.

Takamura, M., Koga, K., Osuga, Y., Takemura, Y., Hamasaki, K., Hirota, Y., Yoshino, O., Taketani, Y., 2009. Post-operative oral contraceptive use reduces the risk of ovarian endometrioma recurrence after laparoscopic excision. Hum. Reprod. 24, 3042—3048.

Takeuchi, H., Awaji, M., Hashimoto, M., Nakano, Y., Mitsuhashi, N., Kuwabara, Y., 1996. Reduction of adhesions with fibrin glue after laparoscopic excision of large ovarian endometriomas. J. Am. Assoc. Gynecol. Laparosc. 3, 575—579.

Tinkanen, H., Kujansuu, E., 2000. In vitro fertilization in patients with ovarian endometriomas. Acta Obstet. Gynecol. Scand. 79, 119—122.

Troiano, R.N., Taylor, K.J., 1998. Sonographically guided therapeutic aspiration of benign-appearing ovarian cysts and endometriomas. Am. J. Roentgenol. 171, 1601—1605.

Tsolakidis, D., Pados, G., Vavilis, D., Athanatos, D., Tsalikis, T., Giannakou, A., Tarlatzis, B.C., 2010. The impact on ovarian reserve after laparoscopic ovarian cystectomy versus three-stage management in patients with endometriomas: a prospective randomized study. Fertil. Steril. 94, 71—77.

Tsoumpou, I., Kyrgiou, M., Gelbaya, T.A., Nardo, L.G., 2009. The effect of surgical treatment for endometrioma on in vitro fertilization outcomes: a systematic review and meta-analysis. Fertil. Steril. 92, 75—87.

Tsujioka, H., Inoue, Y., Emoto, M., Sadamori, R., Shirota, K., Hachisuga, T., Kawarabayashi, T., 2009. The efficacy of preoperative hormonal therapy before laparoscopic cystectomy of ovarian endometriomas. J. Obstet. Gynaecol. Res. 35, 782—786.

Varol, N., Maher, P., Healey, M., Woods, R., Wood, C., Hill, D., Lolatgis, N., Tsaltas, J., 2003. Rectal surgery for endometriosis-should we be aggressive? J. Am. Assoc. Gynecol. Laparosc. 10, 182—189.

Vercellini, P., Vendola, N., Bocciolone, L., Colombo, A., Rognoni, M.T., Bolis, G., 1992. Laparoscopic aspiration of ovarian endometriomata, effect with post operative gonadotropin releasing hormone agonist treatment. J. Reprod. Med. 37, 577—580.

Vercellini, P., Frontino, G., De Giorgi, O., Aimi, G., Zaina, B., Crosignani, P.G., 2003. Comparison of a levonorgestrel-releasing intrauterine device versus expectant management after conservative surgery for symptomatic endometriosis: a pilot study. Fertil. Steril. 80, 305—309.

Vercellini, P., Somigliana, E., Daguati, R., Vigano, P., Meroni, F., Crosignani, P.G., 2008. Postoperative oral contraceptive exposure and risk of endometrioma recurrence. Am. J. Obstet. Gynecol. 198, 504.e1—504.e5.

Wong, B.C., Gillman, N.C., Oehninger, S., Gibbons, W.E., Stadtmauer, L.A., 2004. Results of in vitro fertilization in patients with endometriomas: is surgical removal beneficial? Am. J. Obstet. Gynecol. 191, 598—607.

Wyns, C., Donnez, J., 2003. Laser vaporization of ovarian endometriomas: the impact on the response to gonadotrophin stimulation. Gynecol. Obstet. Fertil. 31, 337—342.

Yanushpolsky, E.H., Best, C.L., Jackson, K.V., Clarke, R.N., Barbieri, R.L., Homstein, M.D., 1998. Effects of endometriomas on oocyte quality, and pregnancy rates in in vitro fertilization cycles: a prospective, case-controlled study. J. Assist. Reprod. Genet. 15, 193—197.

Yap, C., Furness, S., Farquhar, C., Rawal, N., 2004. Pre and post operative medical therapy for endometriosis surgery. Cochrane Database Syst. Rev. 3, CD003678.

Yaron, Y., Peyser, M.R., Samuel, D., Amit, A., Lessing, J.B., 1994. Infected endometriotic cysts secondary to oocyte aspiration for in-vitro fertilization. Hum. Reprod. 9, 1759—1760.

Yazbeck, C., Madelenat, P., Ayel, J.P., Jacquesson, L., Bontoux, L.M., Solal, P., Hazout, A., 2009. Ethanol sclerotherapy: a treatment option for ovarian endometriomas before ovarian stimulation. Reprod. Biomed. Online 19, 121—125.

Zanetta, G., Lissoni, A., Dalla Valle, C., Trio, D., Pittelli, M., Rangoni, G., 1995. Ultrasound-guided aspiration of endometriomas: possible applications and limitations. Fertil. Steril. 64, 709—713.

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