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REVIEW

A new approach to the management of ovarian endometrioma to prevent tissue damage and recurrence

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Abstract Management of ovarian endometrioma is a matter of debate between those advocating early treatment and those believing that cysts less than 3 cm in diameter should not be submitted to surgery. To explore a new approach to its management capable of preserving future fertility, the molecular pathology of ovarian endometrioma is reviewed and mechanisms by which the endometrioma progressively affects the ovary during reproductive life are summarized. The scope of new therapeutic modalities includes restoring the progesterone receptor ratio using progestin or progesterone receptor modulators and decreasing local oestrogen production through an aromatase inhibitor. In addition, free radical production can be blocked by antioxidants and the autophagic process by increasing apoptosis. Finally, metalloproteinases and relaxin activity, as well as the inflammatory process can be controlled. Many of these pharmacological treatments lend themselves to local administration and can be applied through intracystic drug administration; in fact, the intracystic route has already been tried with recombinant interleukin-2, methotrexate and ethanol; the latter to obtain sclerotization. Specifically, it is proposed that endometrial growth in the endometrioma is suppressed by intra-cystic application of synthetic progestins, such as levonorgestrel or danazol, selective progesterone receptor modulators, such as mifepristone, ulipristal or asoprisnil, without affecting ovarian activity.

KEYWORDS: follicle reserve, intracystic drug administration, ovarian endometrioma

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Introduction

Endometriosis is considered a common gynaecologic disease; however, its true incidence has never been firmly determined in the general population of reproductive-age women. The situation is even worse in the case of the specific variant affecting the ovaries (the ovarian endometrioma): not a single epidemiological study exists on its incidence in the various stages of a woman's life. Moreover, it has recently been shown that an ovarian endometrioma may develop in adolescent girls and even before menarche (Brosens et al., 2014), supporting the view that early onset endometriosis, including ovarian disease, may develop by shedding of endometrial stem cells during neonatal uterine bleeding (Gargett et al., 2014). The presence of an ovarian endometrioma may also affect fertility (Berlanda et al., 2015), although overall pregnancy rates seem unaffected after IVF (Gupta et al., 2006). Unless treatment is established at an early stage, almost every surgical intervention to eliminate an endometrioma is bound to decrease ovarian reserve and is often followed by recurrence which, if submitted to repeated surgery, will inevitably cause important damage (Muzii et al., 2015). At present, no consensus has been reached on the timing of surgery in young women; whether surgery should be delayed in infertile women planning IVF is still debated (Ruiz-Flores and Garcia-Velasco, 2012). Therefore, ways to inactivate ovarian endometriomas without affecting a young woman's fertility potential need to be designed.

In this review, the molecular pathology of the ovarian endometrioma, and novel options for a conservative management, are explored in the light of presently available pharmacological treatments that may lend themselves to local administration.

Pathogenesis: a possible guide for medical treatments

Gross pathology

Over the past 2 decades, important advances have been made in our understanding of the pathogenesis of ovarian endometriomas. Brosens *et al*. (1994, 1996) used ovarioscopy for in-situ exploration of the ovarian endometrioma in infertility patients to describe the features of the cystic structure of the ovarian endometrioma. During ovarioscopy, two types of endometriomas can be distinguished on the basis of vascularization and pigmentation of the cavity lining. First, the endometrioma with a pearl-white or yellowish-pigmented cortex, lined by a thin angiogenic mucosa (red endometrioma) and, second, the endometrioma with a dark, pigmented fibrotic tissue (black endometrioma). The red type is lined by highly angiogenic endometrial-like tissue. The brown-black type is lined by fibro-reactive tissue with hemosiderin-loaded macrophages and shows endometrial-like tissue in only 14% of cases. In a study of 19 recurrent chocolate cysts, the diagnosis of endometriosis could be confirmed by ovarioscopy-guided biopsies in 27% of the subjects (Brosens et al., 1994). None of them had a mucosa-like lining, but three (16%) had an enclosed glandular and stromal lesion and two (11%) showed a cortical lining. Occasionally, the endometrioma is connected to a corpus luteum, and may show early colonization by endometriotic surface epithelium.

Cortical and interstitial changes

Several mechanisms by which the endometrioma progressively affects the ovary during reproductive life have been identified.

Nieminen (1963, 1964) conducted a systematic study of the vascular hormonal response and distinguished different reactions according to the cellular structure. Bleeding was likely to occur in the free mucosa-like implant at the site of invagination and in the mucosa-like lining of invaginated cortex. Similar to what happens in eutopic endometrium, the basal layer is the site of active cyclic metaplasia of stromal cells into myo-fibroblasts and *vice versa* (Fujii et al., 1989), and a source of factors, such as endothelins and prostaglandins that modulate the response of underlying junctional zone myometrium to ovarian hormones (Bacon et al., 1995).

It has been shown that human decidual stromal cells express alpha-smooth muscle actin and show ultrastructural similarities with myo-fibroblasts (Oliver et al., 1999); specifically, Fukunaga (2000) documented the presence of smooth muscle metaplasia in ovarian endometriomas and Anaf et al. (2000) demonstrated the presence of smooth muscles in endometriotic lesions originating from four different pelvic locations, including the ovary. Qiu et al. (2012) used transvaginal colour Doppler to describe interstitial devascularization in the ovarian endometrioma bed and confirmed that fibrosis and microvascular injury were a potential cause of reduced follicle reserve.

A recent biopsy study of healthy cortex from ovaries affected by endometriomas (≤4 cm) and contralateral ovaries without cysts reported that cortex from ovaries with endometriomas contained significantly more morphologically atretic early follicles than cortex from contralateral ovaries without cysts (Kitajima et al., 2014). Sanchez et al. (2014) conducted a comprehensive search to identify human studies published on cellular and molecular characterization of the various endometrioma components. They reported levels of free iron in endometriotic cystic fluid that are much higher in comparison with normal serum levels and other ovarian cysts. The cystic fluid causes substantial changes in the lining cells that it baths from gene expression modifications to genetic mutations. The authors concluded that sufficient evidence supports a deleterious effect of the cystic fluid on the adjacent ovarian cortical tissue, independent of the mere mechanical stretching owing to its fluid content.

Molecular aspects of the lining endometrium

It has been known for some time that at a molecular level stromal and epithelial endometriotic cells are different from eutopic endometrial cells (Brosens et al., 2014). A disrupted oestrogen–progesterone receptor expression is linked to genetic and epigenetic changes leading to an increased oestrogen receptor activity, local oestrogen production via aromatase activity and a progesterone resistance (Nisolle et al., 1997). The whole genome DNA microarray shows that

100 genes are differently expressed by two- or three-fold in ectopic versus eutopic endometrium and are associated with inflammation, cell adhesion and remodelling of extracellular matrix (Borghese et al., 2008; Eyster et al., 2007). Intriguingly, up-regulation of the highly conserved homeobox (HOX) genes which control embryonic development is associated with ovarian cancer, whereas a down-regulation of *Hox-A* and *Hox-B* has been shown in endometriosis, suggesting a type of protection against malignant degeneration (Cheng et al., 2005). Furthermore, genes involved in the cell cycle are down-regulated in endometriomas, suggesting that this cell population is quiescent and non-dividing (Borghese et al., 2008).

Of importance for possible treatment is a remarkable activation of the autophagic process; this has been evaluated by means of functional parameters, i.e. a significant increase of lipidated LC3-II protein levels and LC3-II/LC3-I ratio, and a significant decrease of the autophagic substrate SQSTM1 (p62) protein (Allavena et al., 2015). Invasiveness of endometrioma cells is increased by some adhesion molecules, such as CD44 and E-cadherin (Darai et al., 1998), as well as by an augmented remodelling of extracellular matrix, caused by a higher level of metalloproteinases MMP-1 and a lower level of the tissue inhibitor of metalloproteinase-1 (TIMP-1) (Mizumoto et al., 2002). Igarashi et al. (2013) recently reported that an up-regulation of matrix metalloproteinases resulting in an increased ability of endometriotic cells to invade peritoneal organs is mediated by tenascin, a glycoprotein with the ability to modify cell adhesion.

An increased concentration of urokinase plasminogen activator, PAI-1 and PAI-2, molecules with a remarkable degradation capacity, has been described (Boss et al., 2002). MMP-2 and MMP-9 production is further stimulated by activin A, a growth factor whose increased expression influences cellular growth, differentiation and invasion (Florio et al., 2009; Reis et al., 2001). Follistatin, an activin regulator, is overexpressed in endometrioma and hyper-secreted in serum; as such, it has been suggested as a possible serum marker for endometriomas (Florio et al., 2009).

Also, neuropeptides related to corticotrophin-releasing hormone are expressed by endometrial cells. In particular, endometriomas express urocortin, the concentrations of which are elevated in serum, suggesting a role as serum marker (Florio et al., 2007). Members of the same family, Ucn2 and Ucn3, are also expressed by endometriomas; they modulate tumour necrosis factor alpha and interleuikin 4 secretion and participate in the inflammatory events (Novembri et al., 2011). Indeed, an impaired production of pro-inflammatory cytokines modifies follicular function (Bedaiwy et al., 2007) and ovarian reserve (Opoien et al., 2013). Relaxin is another aberrantly expressed gene in endometriotic cells, regulating MMPs and vascular endothelial growth factor (Morelli et al., 2009).

Therefore, according to these multiple pathogenetic mechanisms, new medical treatments for endometrioma may be proposed to restore progesterone receptors A and B ratio by progestin or selective progesterone receptor modulators (SPRM); decrease the local oestrogen production by aromatase inhibitors; block free radical production by antioxidants; inactivate the autophagic process to increase apoptosis; block metalloproteinases and relaxin; block inflammation by corticotrophin-releasing hormone antagonists and anti-inflammatory cytokines.

The effect of intracystic application of any of the already tested (rIL-2 or methotrexate) or new drugs hormonal (progestogens or SPRM) or non-hormonal (antiproliferative, anti-inflammatory, pro-apoptotic) drugs is expected to be the same as when they are systemically administered. It is expected, however, that the close delivery and direct contact with endometriotic cells will facilitate their action at a lower dose, thus reducing the side-effects (also in view of their limited access to the vascular system).

Routes of administration for medical treatment

A variety of agents with the potential for topical use in the medical treatment of the ovarian endometrioma have been tested, mostly in preliminary trials. Both the direct intrauterine and the subdermal constant delivery systems have been explored with promising results. In particular, the intrauterine route using the Intrauterine System Mirena©, first explored by Vercellini et al. (1999), results in a local concentration of levonorgestrel greater than plasma levels, significant amounts delivered into the peritoneum, a superior effectiveness, limited adverse effects and an increased patient compliance during long-term treatment (Lockhat et al., 2005; Vercellini et al., 2005). Therefore, it can be expected that even better results may be obtained by delivering progestogens directly into the cyst.

Here, attention will be focused on the direct, intracystic administration, capable, in our view, of significantly improve results.

Recombinant interleukin-2

Pellicer et al. (1998) showed the existence of a different cytokine regulation in women with endometriosis, with a characteristic increase in interleukin-6 production. This indicates that the endocrine, paracrine, and autocrine milieu is different in these patients. Therefore, based on the premise that decreasing cytokine production within the endometrioma's milieu will be beneficial, Acién et al. (2003) proposed to inject 600,000 IU of recombinant interleukin-2 (rIL-2) in the cysts.

They conducted a double-blind, randomized-controlled trial to evaluate the results of ultrasound-guided aspiration of endometriomas under the effect of gonadotrophin-releasing hormone (GnRH) analogues and a possible additional beneficial effect by leaving 600,000 IU of rIL-2 in the cysts. Twenty-four women with endometriomas larger than 3 cm at transvaginal ultrasonography were included. Although the rates of recurrence of endometriomas 3 cm or larger were similar in both groups, the period until recurrence was significantly greater when rIL-2 was used. In a second prospective and randomized clinical trial, the same group (Acién et al., 2005) used transvaginal ultrasound-guided drainage of endometriomas under the effect of GnRH analogues, to investigate the therapeutic results of one dose of 3 million IU of rIL-2 left intracyst (group I) compared with two doses with a 1-month interval (group II). They found fewer recurrences and a longer interval before recurrence after two doses, but differences were

not significant. They concluded that treatment of endometriomas with transvaginal ultrasound-guided drainage and rIL-2 left in the cysts under endometrial suppressive therapy with GnRH analogues has beneficial effects, improving clinical manifestations and avoiding some surgical interventions. The use of a higher dose of rIL-2 did not produce better results, whereas drainage plus rIL-2 twice had a better effect. In a third prospective and randomized clinical trial including 25 consecutive patients, Acién et al. (2010) conducted two transvaginal ultrasounded-guided punctures, leaving 3 million IU of rIL-2 in the aspirated cysts once (group I) or on both punctures (group II) according to randomization. After 1 year, 20% (group I) and 73% (group II) of the patients had to undergo surgery; after 2 years, these numbers were 55 and 82%, respectively. The investigators concluded that treatment of endometriomas with transvaginal ultrasound-guided drainage and rIL-2 left in the cysts, without using endometrial suppressive therapy with GnRH analogues as in previous studies, has low efficacy. Recurrences were even more frequent after the use of two rIL-2 doses.

Velasco et al. (2005) determined the changes in cytokine levels of patients with ovarian endometriomas after treatment with gonadotrophin-releasing hormone analogue, ultrasound-guided drainage, and intracystic injection of dextrose that did or did not contain recombinant interleukin-2. The study showed that intracystic IL-2 administration resulted in a decrease of the cytokine production. Although the results were important for the design of future treatments using immunomodulation, further clinical testing has not been carried out.

Methotrexate

Mesogitis et al. (2000) carried out an ultrasonographically guided drainage of ovarian endometriomas, followed by direct injection of methotrexate into the collapsed cyst. They believed that, given its usefulness in blocking the development of ectopic pregnancies, it was worthwhile trying methotrexate in ovarian endometriomas.

Agostini et al. (2007) described the ultrasound-guided puncture and aspiration of recurrent endometriotic cysts followed by methotrexate injection as an alternative to surgical treatment. This drug was selected because of its low toxicity combined with high cytolytic effect when used for ectopic pregnancy. They also mentioned that, as methotrexate injection is intracystic, diffusion in the rest of ovary would be limited; finally, in their experience, in-situ methotrexate injection for ectopic pregnancy had never shown ovarian damage. They reported no complication in 14 procedures. After a mean follow up of 20 ± 5 month (minimum: 13, maximum: 29), four recurrences were diagnosed (28.6%). Two asymptomatic recurrences were not treated and two painful recurrences underwent second cyst drainage with methotrexate injection. In a randomized controlled trial of transvaginal ultrasound aspiration versus aspiration and in-situ methotrexate injection involving 202 patients with ovarian endometrioma, Shawki et al. (2011) investigated the efficacy and safety of the in-situ methotrexate injection. Of 210 patients, 188 were available for follow-up. The overall success rate after complete follow-up was 54.7% in group I compared with 86.0% in group II. In study group I, 25 participants (26.3%) needed single aspiration, 14 (14.7%) required two, and 13 (13.6%) needed three aspirations; this was compared with 62 patients (66.6%) needing a single injection, 11 (11.8%) requiring two, and seven (7.5%) requiring three injections in group II; this represented a statistically significant difference ($P < 0.05$). The cyst size and volume of fluid aspirated were statistically significant factors in the resolution of the cyst ($P < 0.05$), whereas patient's age was not. The authors concluded that transvaginal ultrasound-guided aspiration and in-situ methotrexate injection is a simple, safe, non-invasive and effective treatment in selected cases of ovarian endometriomas, with good acceptability among patients (Shawki, 2012). The investigation of the effect of in-situ methotrexate injection on ovarian response and reproductive outcomes in IVF cycles showed no statistically significant difference between the number of oocytes retrieved, fertilization rate and quality of the embryos obtained from the aspirated ovary and reproductive outcomes. Six months was enough as washout period of the drug before conception and was considered advisable to prevent the chance of chromosomal abnormalities in the offspring.

Ethanol sclerotherapy

In a retrospective study of 108 women with recurrent cysts, Hsieh et al. (2009) evaluated the effectiveness of transvaginal ultrasound aspiration and ethanol sclerotherapy. The 1-year recurrence was significantly lower than in the control group, showing that retention of ethanol is more effective than irrigation only. Following this finding, Gatta et al. (2010) investigated whether ultrasound-guided aspiration followed by ethanol sclerotherapy could be used in treating endometrial cysts as an alternative to surgery. In 50 consecutive patients with an average age of 25.5 years (range 16–40 years) and an ultrasound diagnosis of endometrial cysts, ultrasound-guided aspiration of a total of 54 cysts followed by ethanol therapy was carried out. The procedure was successful in all cases and the follow-up covering 1 year showed after 12 months four (8%) recurrences, three of them opting for a second session of ultrasound-guided aspiration and ethanol sclerotherapy. The study suggests that ultrasound-guided aspiration and sclerotherapy provide a valid alternative to surgery in treating endometrial cysts particularly in the young woman.

Wang et al. (2011) enrolled 198 patients and divided them into three groups. In group 1, the saline washing group, the cavity of the cyst was washed thoroughly with warm saline. In group 2, the ethanol short-time retention group, after washing with saline, the cyst was injected with 95% ethanol with a volume of one-half of the fluid aspirated from the cyst. Ten minutes later, the rest of the ethanol was aspirated. In group 3, the ethanol retention group, the procedures were the same as with the ethanol short-time retention group, except that 95% of the ethanol was retained in the cyst. An ultrasound examination was carried out in the third, sixth and twelfth month after therapy. The chocolate cyst cure rate was significantly higher in the ethanol retention group (66/69 [96%]) than in the ethanol short-time retention group (56/68 [82%]) and no case was cured in the first group (saline washing). They concluded that ultrasound-guided injection and 95% ethanol retention are an effective therapy for the treatment of postoperative recurrent chocolate cysts.

The efficiency of transvaginal aspiration accompanied by ethanol sclerotherapy for treating cyst recurrence in patients who have previously undergone surgery was evaluated by Chang et al. (2013) in a large group of 196 patients with endometrioma recurrence. Patients were followed-up at 3, 6, and 12 months to detect complications, determine the size and persistence of cysts, obtain the pelvic pain score, and assess for pregnancy or the need for repeat surgical intervention. Cyst size was consistently reduced until 6 months after ethanol sclerotherapy. The mean (SD) cyst reduction rate was 37.2% and the pain score reduction rate was 20.5%. The antral follicle count was simultaneously increased by 36.4%.

The question can be raised whether the sclerotic effect of ethanol instillation can damage the ovarian tissue. This was evaluated in rats by Atilgan et al. (2014) who measured the regression level of a simple ovarian cyst size after local ethanol application and the damage level of adjacent ovarian reserve. They found that local ethanol application reduces cyst diameter, but concomitantly decreases ovarian reserve due to increased fibrosis; for this reason, they recommended that intracystic ethanol application should be carried out cautiously in humans.

Future of intracystic approach for treatment of endometriomas

The working hypothesis for future improvements in local intracyst treatment is that endometrial growth in the endometrioma can be suppressed by direct application of synthetic progestins, such as levonorgestrel (LNG) or danazol, or of selective progesterone receptor modulators (SPRM or PRM), such as mifepristone, ulipristal or asoprisnil, without affecting ovarian activity.

The most obvious group of substances that could be used for an intracystic treatment are progestins. Wildemeersch et al. (2002) used a 'frameless' intrauterine drug delivery system (FLDDS; Applied Controlled Release (APCOR), Ghent, Belgium) that releases LNG to successfully treat endometrial hyperplasia. Interestingly, the authors reported that the FLDDS releasing 14 μg/day of LNG was used to treat non-atypical and atypical endometrial hyperplasia in 12 women (Wildemeersch and Dhont, 2003). Over 3–4 years of follow-up, the cure rate was 100%, as confirmed by repeat endometrial biopsy. Formal evaluation of the system in tamoxifen users (to protect the endometrium), or in women with rectovaginal endometriosis, has just begun, and early results suggest that the system will also be suitable for these indications. It seems, therefore, that a frameless device can be anchored in the wall of the cyst, similarly to what occurs in the uterine cavity, for intracystic drug release to prevent regrowth, recurrent endometrial bleeding, as well as malignant transformation.

Another class of drugs that might be used to inactivate ovarian endometriomas, because they effectively inhibit endometrial proliferation and reduce endometriotic lesions in animal models (Bouchard et al., 2011), are selective progesterone receptor modulators (SPRMs or PRMs). These drugs, however, produce endometrial changes following medium- to long-term (3 to 6 months) continuous daily dosing (Benagiano et al., 2014). Specifically, mifepristone and asoprisnil have been shown to cause unusual changes termed 'progesterone receptor modulator-associated endometrial changes' (PAECs) characterized by dilated, weakly secretory endometrial glands with few mitotic figures, and stromal effects ranging from compaction to non-uniform oedema (Mutter et al., 2008; Williams et al., 2007). Although a group of pathologists concluded that the changes revealed nothing worrying, they should be considered a safety concern and a *Dictionary of endometrial biopsy diagnoses for clinical trials with SPRMs* was developed to supplement conventional criteria (Mutter et al., 2008). Long-term studies are needed, especially if SPRMs are to be used for more than 3 months.

Little is known on the effect of SPRM on endometriosis: a recent review summarized work by Chinese scientists and clinicians with mifepristone and analysed more than 100 articles; unfortunately, most of these publications are of low quality and cannot be used to show that mifepristone is truly efficacious (Guo et al., 2011).

In conclusion, management of ovarian endometriomas remains one of the major challenges in reproductive medicine for several reasons. First, diagnosisis is delayed. In contrast, with deep pelvic endometriosis, the ovarian endometrioma may occur during adolescence in the absence of any specific symptoms. Second, the pathology of the endometrioma is complex as, contrary to intra-ovarian cysts, no proper wall separates the cystic structure from normal ovarian tissue. Third, the progression of ovarian pathology inevitably involves the extension of peri-ovarian adhesions, increase in the cyst size with its chocolate content, or presence of haemorrhagic luteal cysts and progressive smooth muscle metaplasia of the ovarian interstitial tissue. Consequently, surgical management may cause additional damage with loss of follicular reserve and surgical adhesions.

For all the above-mentioned reasons methods for developing the intracystic application of hormonal and non-hormonal drugs are needed, especially for young patients with endometrioma. This strategy will reduce the use of present surgical treatment modalities, which carry a distinct risk of reducing ovarian reserve. In addition, the proposed new therapeutic approach will reduce, if not eliminate, side-effects caused by the systemic administration of these drugs, and will probably shorten its duration, hopefully making the procedure less expensive.

For these reasons, a new approach is proposed that can be applied at an early stage in adolescents and young women.

The following potential benefits can result from the regression of the cyst's endometrial-type lining: in the short term, there should be an inactivation and involution of the endometrial lining, the absence of intra-cystic cyclic bleeding and a reduction of the size of the cyst; in the long term, inactivation of the endometrial-like lesions should prevent further damage of the follicle reserve by the progressive muscle metaplasia, fibrosis and devascularization in the subcortical interstitial tissue.

Possible additional benefits may also ensue, such as the suppression of endometrioma lining activity without affecting the menstrual cycle. Finally, surgery can be delayed while IVF can be planned, as well as maintenance of the prospects of natural conception;

In the presence of a luteal cyst, the procedure will allow its spontaneous regression, irrespective of whether the luteal cyst may be communicating or not. Finally, during pregnancy, both infection (Phupong et al., 2004) and rupture (Barbazan et al., 1993; García-Velasco et al., 1998;

Jiménez-Castillejo and Reyna-Villasmil, 2012; Rossman et al., 1983; Vercellini et al., 1992) of the endometrioma have been reported; therefore, the question can be raised whether the current policy of no-surgery before IVF increases the risk of complications such as rupture and abscess during pregnancy. With the proposed system, the risks of infection or rupture during pregnancy can be avoided without surgery.

Only future comparative clinical trials will reveal which of the currently or future drugs used in patients with endometriosis will be the most effective when administered locally in the cystic endometrioma's cavity.

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