Clinical management of endometriosis
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Chapter 9

Discussion and general conclusions
The purpose of this thesis was to gain new insights on the clinical management of endometriosis. We aimed to explore the potential role of COC in hormonal management of ovarian endometriomas and DIE. We investigated the clinical/surgical outcomes of patients undergoing segmental bowel resection for colorectal endometriosis. We studied the effect of DIE surgery on Quality of life and the quality of sexual functions in surgically-managed patients. In addition, we evaluated the performance of peripheral blood markers for diagnosis and follow up of endometriosis.

COC and Endometriosis

A critical concern in the management of endometriosis is the possibility of preventing recurrences after conservative surgery. This is particularly important when ovarian endometriomas are excised. It is known that the presence of ovarian endometriosis cysts, as well as their removal, may be detrimental for future fertility (1,2). Endometrioma recurrence is increasingly recognized as relatively common. In the recent literature, data are accumulating on actual post-operative endometrioma recurrence rates, which vary between 30% and 50% after 2–5 years (3-7).

Endometriosis surgery, although considered cytoreductive, is not curative. Hence, long-term therapeutic strategies should be based on factors influencing the natural history of the disease and its tendency towards reappearance. By the studies I and II, we aimed to evaluate the role of postoperative COC therapy in prevention of anatomical relapse/symptom recurrence in patients who underwent ovarian endometrioma excision.

Reviewing the recent literature, there is a growing body of evidence supporting that postoperative COC exposure can be associated with a substantial reduction in the risk of ovarian endometriosis recurrence (8). However, the type of COC, regimen and duration of treatment, as well as parameters for diagnosing recurrence are not yet well defined. Some studies assessed anatomical recurrence (5,7), others evaluated pain recurrence (9,10) and one study considered both (11).

Details of the studies are summarized in Table I. (8)
<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Type of study</th>
<th>N° Patients</th>
<th>Medical Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muzii et al 2000</td>
<td>Anatomical and pain recurrence</td>
<td>RCT</td>
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</tr>
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<td></td>
<td></td>
<td></td>
<td>33</td>
<td>Cyclic COC</td>
</tr>
<tr>
<td>Vercellini et al 2003</td>
<td>Pain recurrence</td>
<td>Prospective self-controlled</td>
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<td>Continuous COC</td>
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<td>Koga et al 2006</td>
<td>Anatomical recurrence</td>
<td>Retrospective</td>
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<td>none</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15</td>
<td>COC</td>
</tr>
<tr>
<td>Sesti et al 2007</td>
<td>Pain recurrence</td>
<td>RCT</td>
<td>110</td>
<td>placebo Continuous COC/GnRH-agonist</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>38/39</td>
<td>Dietary therapy</td>
</tr>
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<td></td>
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<tr>
<td>Vercellini et al 2008</td>
<td>Anatomical recurrence</td>
<td>Cohort study</td>
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<td></td>
<td>231</td>
<td>Cyclic COC</td>
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<td>Thesis Study I</td>
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<td>Cyclic COC</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>95</td>
<td>Continuous COC</td>
</tr>
</tbody>
</table>

Table 1: Designs of the studies. RCT: randomized controlled trial; COC: combined oral contraceptives

Findings from our RCT’s (study I and II) confirmed the results of the prospective cohort study of Vercellini et al, where COC therapy was offered immediately after surgery to patients undergoing laparoscopic excision of ovarian endometriotic cysts and not seeking pregnancy. Of the 277 patients followed up for a mean period of 31 months, 102 used oral contraceptives for the entire follow-up period (always users), 129 used oral contraceptive discontinuously (ever users) and 46 declined treatment (never users). Recurrent endometriotic cysts were detected in 74 subjects (27%). The crude cyst recurrence rate was 9% and 56% in always and never users respectively. The absolute risk reduction of endometrioma recurrence in the ever users compared with the never users was 47% (95% CI 37–57%). (7)

Two studies (Koga et al., 2006; Muzii et al., 2000) demonstrated no association between post-operative use of COC and long-term reduction of disease recurrence. In these studies, however, the duration of treatment should be taken into account (9.5 and 6 months respectively). The lack of
long-term effects, therefore, could be due to discontinuation of therapy more than to a real inefficacy of post-operative oral contraceptives.

Regarding recurrence of endometriosis-related symptoms, our results (study II) are in agreement with other authors in that, not all the types of pain considered seem to be equally responsive to post-operative COC. We demonstrated that dysmenorrhoea, can be successfully controlled by oral contraceptives. Continuous COC can provide early reduction of dysmenorrhoea after 6 months of treatment (10), however cyclic COC need to be administered for at least 18 months to be effective. Furthermore continuous administration seems to be a valuable option for dysmenorrhoea that does not respond to cyclic use of COC. As regards endometriosis-related dyspareunia, there is no evidence of a positive effect of post-operative COC on its reduction. Furthermore, Sesti et al. demonstrated that placebo seems to be more effective than hormonal therapy in relieving this type of pain. They explained this finding by the fact that dyspareunia perception may be influenced by psychological factors depending on woman personality, marital and psychosexual issues (10).

Regarding chronic pelvic pain, there is no agreement about the effects of post-operative COC. We did not find differences between patients treated with COC and untreated patients in terms of chronic pelvic pain recurrence, although Sesti et al. (2007) found significant differences in favor of post-operative COC use (10). The more evident benefits achieved with oral contraceptives on dysmenorrhoea in comparison with dyspareunia and chronic pelvic pain can be explained by the fact that dysmenorrhoea can be related to endometrial bleeding, that can be decreased or suppressed by COC, although other types of pain are possibly due to different physiopathologic mechanisms. Although efficacy of COC in prevention of dyspareunia and chronic pelvic pain has not yet been clearly defined in the literature, our data (study II) confirmed that COC are effective in restraining aggravation of these types of pelvic pain. A clear distinction, however, must be made between short- and long-term post-operative adjuvant treatments. The benefit is usually observed during oral contraceptive use and the protective effect tends to vanish rapidly after discontinuation (12).

Our results (study III) demonstrated that in cases of posterior DIE, COC therapy can be beneficial for pain control and may be valuable in suppressing disease progression. Although not widely accepted among endometriosis experts, hormonal treatment seems to be significantly able to reduce pelvic pain in cases of DIE (13). We noticed that COC hormonal treatment does not lead to the complete disappearance of deep endometriotic nodules, but rather to a decrease in their progression. This observation is consistent with data concerning the histological composition of deep nodules shown to consist of only 20–30% of endometrial epithelium, while 60% is fibrosis and smooth muscular fibres insensitive to hormone action (14). However, a non-significant decrease in volume associated with the suppression of cyclic intra-nodular micro haemorrhages might be enough to relieve pain significantly as long as the treatment is administered (15).
In conclusion, from the first part of this thesis we demonstrated that when the diagnosis of non-complicated ovarian or deep infiltrating endometriosis is confirmed, endocrine pharmacotherapy, with COC, can be used as a neo-adjuvant or adjuvant measure. Long-term administration of COC seems to be a valuable adjuvant post-operative measure in women undergoing conservative surgery for symptomatic endometriosis. Since both continuous and cyclic administrations seem similarly effective in reducing endometriosis recurrence, the choice of the regimen can be modulated according to patient preferences.

We have to underline that the COC mainly focus on inhibiting estrogen and its receptors which are not useful for every patient with endometriosis because estrogen is only one factor in the development of endometriosis. Understanding endometriosis signaling pathway is essential and makes it possible to develop an effective non-hormonal medications which could not only decrease estrogen level but also inhibit inflammation and angiogenesis. Furthermore, sufficiently powered RCTs, evaluating molecular basis of action of COC, with a long-term therapy and a long follow-up period, are needed to provide recommendations regarding the COC administration regimens and the specific combinations to be used.

**Surgery and Deep Infiltrating Endometriosis**

Surgical treatment of DIE may be a difficult choice as patients are young, professionally active and plan to conceive. Balancing between extended excision and maximum organ conservation is a real challenge. The concept of “Conservative-Radical” surgery for endometriosis is getting widely accepted among endometriosis experts. The decision to perform segmental bowel resection for patients having colorectal endometriosis is supported by evidence of significant improvement in pain symptoms and in patient quality of life, shown by the results of retrospective studies on women exclusively managed by this procedure (16-19).

Nonetheless, surgical morbidity and functional damage appear to be high in women managed by segmental colorectal resection (18, 20-22). Despite the extended radical excision practiced by many surgeons, aiming to decrease the incidence of endometriosis recurrence, microscopically complete resection is a rare reality (20, 23,24). In addition, there is no strong evidence that segmental rectal resection prevents post-operative pain recurrence (25).

Though the retrospective design of our study (IV), bearing in mind the possible methodological weakness inherent to it, we observed no statistically significant differences in terms of anatomical and pain recurrence, pain symptoms and quality of life improvement among the patients with or without positive margins, satellite lesions and different degrees of vertical infiltration of the rectal wall. Furthermore, women with or without satellite lesions did not have any significant differences
in terms of preoperative VAS of pain symptoms and SF-36 scores. We could conclude that for patients with colorectal endometriosis, indicated for segmental resection, it would be more beneficial to curtail rather than encourage aggressive rectal excision.

*Outcomes of DIE surgery/ surgery followed by COC therapy*

It has been recently demonstrated that endometriosis impairs health related quality of life (HRQol) and work productivity across countries and ethnicities (26).

In terms of sexual function outcomes, we demonstrated (in study V) that sexual desire, satisfaction with sex and pelvic problem interference with intercourse, are significantly improved after 6 months from laparoscopic excision of DIE followed by postoperative COC therapy. In addition, no difference in sexual outcomes was detected between patients submitted to intestinal resection and nodule excision, in cases of Bowel endometriosis. These results confirm the findings that when radical laparoscopic excision of endometriotic lesions is performed following nerve-sparing rules, this might not negatively interfere with sexual functions.

Considering QOL, our results (study VI) are in agreement with the finding that surgery of endometriosis, especially in its deep form improves QOL. In our study, however, we did not find any significant difference in all SF-36 scores between patients submitted to the surgical treatment alone and patients who received six-month postoperative COC treatment. There was no statistically significant difference between patients with colorectal endometriosis submitted to intestinal segmental resection or intestinal nodule shaving.

*Non-invasive markers for early detection and follow-up of endometriosis*

Laparoscopy is still considered the “gold standard” for endometriosis diagnosis. The availability of a non-invasive test may allow early diagnosis and accurate follow-up, as well as clinical intervention to mitigate progression of the disease. A reliable molecular, or genetic marker that can be differentially expressed in endometriosis, or its subtypes, may be clinically used to develop a non-invasive diagnostic test for endometriosis. This diagnostic test should ideally have good sensitivity and specificity as well as satisfactory positive and negative predicative values for the detection of endometriosis, and has also to be cost effective and readily available. The ideal non-invasive endometriosis marker does not yet exist. CA-125 is a widely used serum marker in clinical practice, for the diagnosis and evaluation of recurrent endometriosis or the success of a surgical treatment. A meta-analysis including twenty three studies and assessing the diagnostic performance of serum CA125 has shown that it is a poor diagnostic method with 90% specificity and 28% sensitivity (27). A combination of available markers may increase the overall accuracy. In our study
(study VII), we measured the mRNA level of Survivin in the peripheral blood in women with and without endometriosis. We demonstrated that the combination of the three markers (CA 125, Ca19-9 and Survivin) yielded a higher sensitivity than that obtained by single marker analysis.

**Future perspectives**

Endometriosis remains a difficult clinical problem and warrants more extensive research to understand the disease pathology. The future is to confirm early diagnosis by non-invasive tests using a panel of potential genetic and molecular bio-markers. A long term goal is to be able to identify genetic determinants that contribute to the expression of the different phenotypes seen in endometriosis.

Proteome analysis is now getting widely accepted as a complementary technology to genetic profiling and together enables a better understanding of the diseases and the development of new treatments. Proteomics allow the simultaneous observation of alterations in protein expression that may be either a precursor to or causative in disease development or a consequence of the disease. These techniques check and identify proteins that are expressed differently in patients with endometriosis versus normal controls. More recently, protein arrays using antibodies enable the screening of thousands of proteins against one sample. In future, such arrays could measure the expressions of multiple proteins to reveal changes in their regulation and expression in disease states. Furthermore, by using protein chip arrays, differential analysis of protein expression in women with and without differential protein profiling technology can be developed into powerful tool for endometriosis research. (28,29)

Furthermore, the use of DNA microarrays allows the search for new gene expression markers of endometriosis by identifying differentially expressed genes in endometriosis implants compared with endometrial tissue. The aim is to identify changes in gene expression characterizing the disease state, helping to better understand the disease progression and identify novel therapeutic targets. Genetic markers that are prognostic for endometriosis can be genotyped early in life and could predict individual response to various risk factors and treatment. Genetic predisposition revealed by genetic analysis for susceptibility genes can provide an integrated assessment of the interaction between genotypes and environmental factors, resulting in synergistically increased prognostic value of diagnostic tests. (28,30,31) Thus, pre-symptomatic and early symptomatic genetic testing is expected to be the cornerstone of the paradigmatic shift from late surgical interventions to earlier preventative therapies. Thus, there is an urgent need for novel genetic markers that are predictive of endometriosis and endometriosis progression, particularly in treatment decisions for individuals who are recognized as having endometriosis.
REFERENCES:


