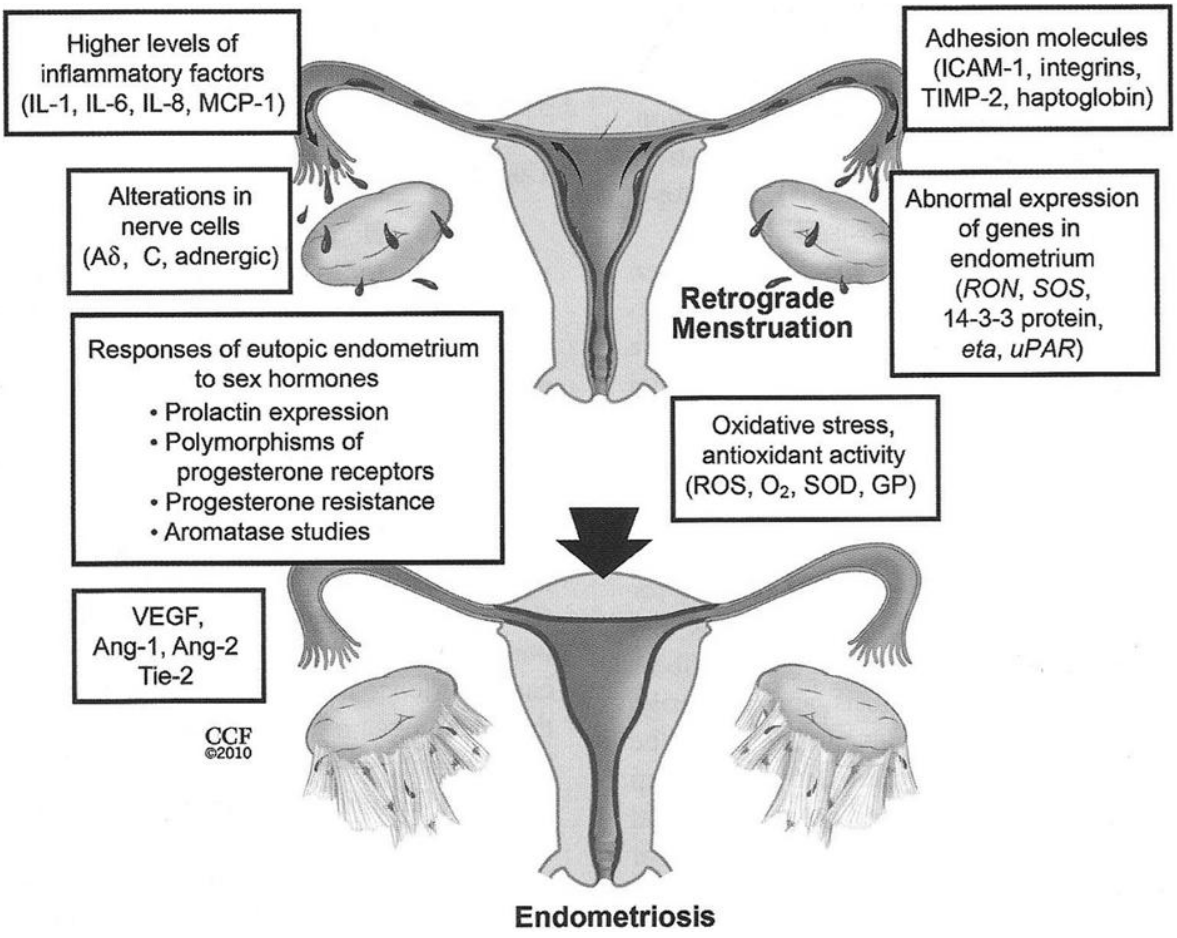
ENDOMETRIOSIS

Most authorities believe endometriosis results from retrograde menstruation and subsequent implantation of endometrial glands and stroma outside of the uterus. This theory was initially advanced in 1927 by Dr. Sampson.[1] This, of course, does not explain all we know today about endometriosis. Current thought process involves impaired immunologic response, genetic predisposition and altered inflammatory component.

Although endometrial cells are structurally the same in women with and without endometriosis, they function differently.[2-5] Endometrial cells of women with endometriosis have different gene expression,[6-9] respond to hormones differently[6,10-12] show different inflammatory and cell adhesion markers,[3,13-17] oxidative stress markers,[18-21] have different nerve properties[22,23] and angiogenic abilities.[24,25]



From Carvalho L, Podgaec S, Bellodi-Privato M, Falcone T, Abrao MS. Role of eutopic endometrium in endometriosis.[26]

Endometriosis is widely studied and imperfectly understood. Endometriosis effects about 10% of all reproductive aged women and is present in one half to two-thirds of women with chronic pelvic pain.[6,26,27] The correlation between amount of endometriosis and degree of pain is low. Not all women with endometriosis have pain.

Medical Management

A variety of therapeutic options are available for endometriosis. Palliation is certainly an option. The patient may or may not elect to use oral analgesics. Endometriosis does not turn to cancer, does not decrease life expectancy, and likely will not progress significantly. Palliation is always an option and must be considered.

Classical therapeutic options include pseudopregnancy and pseudomenopause. These options are based on practical historical observations. First, women with chronic pelvic pain often have relief with menopause when estrogen levels are persistently low. This observation has been largely confirmed in modern medicine when bilateral oophorectomy results in profoundly low estrogen levels and concomitant relief of pain. Second, women with chronic pelvic pain often experienced significant relief with pregnancy and subsequent lactation; in this case estrogen levels were hugely elevated but also in a steady state (without cycling).

Pseudopregnancy options involve maintaining the hormones in an elevated level, but steady state. These include continuous low-dose oral contraceptive therapy, continuous Ortho Evra patches, or continuous use of NuvaRing. Withdrawl on a perhaps q.6-month or q.12-month basis to avoid hyperstimulation to the endometrium may be encouraged.

Women with endometriosis and dysmenorrhea experience greater pain relief with OCs than with placebo.[28]

On the order of 60 – 70% of female chronic pelvic pain sufferers will enjoy relief in symptoms from pseudo-pregnancy treatment regimens. True pregnancy followed by breast-feeding with suppressed ovulation is another therapeutic option.

Pseudomenopause options are confined to drugs such as Danazol and Lupron Depot. The use of either 3.75 mg of Lupron Depot monthly injections for six months or 11.25 mg of Lupron Depot injections on a q3-month basis for a total of two injections is discussed. Add-back therapy is most often recommended to ease the vasomotor symptoms which accompany GnRH therapy in most women. Norethindrone 5 mg could is prescribed on a daily basis to decrease the likelihood of vasomotor symptoms and vaginal thinning related to the hypoestrogenic status induced by the Lupron Depot therapy. Concomitant use of Replens, a synthetic copy of natural human lubricant may prove beneficial in reducing insertional dyspareunia and enhancing coital satisfaction.

OCs significantly reduce dysmenorrhea and pelvic pain associated with endometriosis, but they are less effective than the gonadotropin-releasing hormone (GnRH) analog, goserelin, in reducing dyspareunia.[29]

Danazol is the oldest drug in the pseudomenopause class. Danazol's side occasionally effect tolerability including deepening of the voice, oily skin, acne and growth of unwanted facial hair. These side effects are not related to GnRH Agonist (Lupron) use. Danazol is covered on most formularies, is relatively inexpensive and very efficacious.[30-31]

Current investigation includes vaginally administered Danazol to decrease dose and minimizing androgenic side effects. The likelihood of symptomatic relief for female pelvic pain sufferers is stated as 80 – 90% with pseudo-menopause treatments of at least six months. Pain relief does not happen immediately, however. It often requires four to five months of therapy to notice meaningful improvement. Once achieved, the improvement in pain status may last several years.

Pseudomenopause options may result in a paradoxical increase in pelvic pain around the time they are commenced. This is called a "Flare" response and should be expected. This is short lived and will dissipate over a week or two.

Additional treatment options are also available.

DepoMedroxyProgesterone Acetate (DMPA-SC 104 mg) can be used effectively to treat endometriosis. Excellent resolution of pain complaints is observed with its use.

Levonorgestrel-releasing IUD has also shown to be effective. One study shows pain relief similar to that achieved with Lupron therapy.[32]

Femara (2.5 mg daily) and norethindrone is an alternative to Lupron or can be taken after conclusion of a six-month course of Lupron. Side effects are similar to those of Lupron with hot flushes and vaginal ndryness . Femara is an aromatase inhibitor and works by inhibiting estrogen production within the endometriotic cells themselves in addition to limiting estrogen production in the ovary and fat cells. Femara must be used with either Lupron or estrogen-progesterone contraceptives to suppress follicular cyst formation.

Femara can be used as continuation therapy after six months of Lupron, or by itself. Femara has been shown to be effective for women who have not improved with other treatments.[33]

In the first prospective randomized trial of aromatase inhibitors for endometriosis persisting after conservative surgery, the 2 groups received either a GnRH agonist alone or the GnRH agonist plus anastrozole for 6 months. Over the following 2 years, pain recurrence was significantly less among the combined-therapy group. Early bone loss was more pronounced among patients treated with combination therapy, but bone loss between the groups was roughly equivalent by the end of treatment.[34]

A second study, 16 patients unresponsive to prior treatment received letrozole and a combination OC or norethindrone acetate for 6 months. The median baseline pain score was 7 on a scale of 0 to 10. By the end of treatment, the median pain score was 1.5. Nine patients were evaluated after discontinuation of therapy, and their pain scores returned to pretreatment levels. No correlation was detected between length of treatment and overall improvement in pain score.[35]

A Cochrane database review showed no clear evidence that any medical therapy is superior to another for endometriosis and pelvic pain, with the exception that GnRH analogs may be more effective against dyspareunia.[36]

2006, the Practice Committee of the ASRM recommended that diagnostic laparoscopy confirming endometriosis precede medical treatment, to avoid unnecessary short- and long-term exposure to the adverse effects of GnRH.[37]

All categories of drug therapy work as "a window into the future" to enhance diagnostic precision. Significant symptomatic improvement in pain status yields two benefits. First, there is

actual relief of pain which can last for several years. Second, the knowledge that if significant pelvic pain from endometriosis returns following cessation of treatment, that hysterectomy and bilateral oophorectomy will likely result in symptomatic relief to the point realized as a result of prior drug therapy.

Surgery For Diagnosis and Therapy

Even when an endometrioma is suspected, data do not suggest a benefit to pre-operative medical management.[38]

The benefit of surgery followed by long-term drug therapy, in our opinion, is the most likely therapeutic regimen to result in long-term reduction of pain from endometriosis. This means laparoscopy with destruction or excision of endometriosis (cytoreductive therapy) followed by drug therapy (see above). Laparoscopic excision has been shown to provide significantly greater pain relief than placebo laparoscopy (80% vs 32%).[39]

No evidence suggests that any surgical approach (ie, ablation vs. resection) is superior to another in reducing recurrence rates. In one study, the cumulative 5-year recurrence rate was 19%. Other studies suggest the rate may be much higher. Conservative surgery is preferred, especially for women interested in bearing children.[40]

When endometriosis is detected on diagnostic laparoscopy, immediate surgical excision is warranted.[41-42] Conservative surgery preserves the uterus and as much ovarian tissue as possible. A laparoscopic approach offers advantages over laparotomy, including a shorter duration of hospitalization, anesthesia, and recuperation.[43] Importantly, optical magnification provides better visualization of implants with the laparoscope than with open procedures.

Ancillary procedures to laparoscopy may include presacral neurectomy, uterosacral interruption of sensory nerves innervating the pelvis (LUNA procedure), and uterine suspension to avoid adhesion formation from the posterior cul-de-sac (pouch of Douglas) to the posterior surface of the uterus, tube, and ovaries.

Adding LUNA to laparoscopic surgery did not significantly reduce pain, dysmenorrhea, dyspareunia, or dyschezia. Various meta-analyses of LUNA have confirmed that the procedure performed in conjunction with laparoscopic treatment does not improve pain relief.[44-46]

A randomized controlled trial comparing presacral neurectomy with laparoscopic surgery showed that women in both groups had significantly reduced frequency and severity of pelvic pain, dysmenorrhea, and dyspareunia at 6 and 12 months. At 12 months, severity of symptoms was less in the presacral neurectomy group compared with the laparoscopy group.[47-48]

Pain relief is achieved in most patients who undergo laparoscopic ablation / resection of endometriosis and lysis of adhesions.[49] However, the risk of recurrence is estimated to be as high as 40 percent at 10 years follow-up[50-51] and about 20 percent of patients will undergo additional surgery within two years.[52]

The efficacy of surgical management of endometriosis was demonstrated by two randomized trials that compared the outcome of women who underwent therapeutic laparoscopic surgery with the outcome of women who underwent diagnostic laparoscopy alone or expectant management:

- In the first trial, laparoscopic laser ablation of endometriotic implants plus uterine nerve ablation was more likely to result in improvement or resolution of symptoms at six months than expectant management (63 versus 23 percent).[53]
- In the second trial, laparoscopic excision of implants led to symptomatic improvement in 80 percent of patients at six months compared to 32 percent of controls undergoing diagnostic laparoscopy.[54]

In the first trial,[53] women with stage I disease (a large proportion of study participants) were less likely to improve after their surgical procedure than women with stage II-IV disease. Most of the women in the second trial[54] had stage II-IV disease, which may account, at least in part, for the higher surgical success rate reported in this study.

In many cases endometriosis may exist over the course of the ureters (tubes carrying urine from the kidneys to the bladder). This may or may not lead to urinary tract symptoms or abnormalities found on imaging including hydronephrosis or hydroreter. Ureters are affected in about 1% of cases of endometriosis[55-57] but this increases to 4.4% in cases of deep endometriosis[58]. Ureterolysis to separate the ureter from endometriosis of the parietal peritoneum is feasible in 91% of patients while the remainder require ureteral reimplantation in the bladder.[59]

Definitive surgery involves hysterectomy, with or without removal of the fallopian tubes and ovaries. Definitive, rather than conservative, surgery for treatment of endometriosis should be considered when: 1.) incapacitating symptoms persist following conservative surgery and medical therapy, 2.) moderate to severe disease is present and future pregnancy is not desired, or 3.) hysterectomy is indicated for coexisting pelvic pathology.[60] The decision to perform a definitive procedure is primarily dependent upon the patient's interest in maintaining child-bearing potential. Young women (under the age of 30 years) who undergo hysterectomy are more likely than older women to report residual symptoms, a sense of loss, and overall disruption in their life.[61]

The ovaries may be conserved in younger women to avoid premature development of menopausal symptoms and decisions regarding estrogen replacement. However, removal of both ovaries is appropriate when the ovaries are extensively damaged by endometriosis, or when the woman is approaching menopause. Estrogen replacement, with or without a progestin, to prevent menopausal symptoms should be considered when the ovaries are removed, even when surgery has not removed all endometriotic implants.[61] There is a low likelihood of symptomatic recurrence in these cases of less than five percent.[52] There are few data on recurrence in patients with bowel endometriosis. One study suggested that recurrence rates are higher in these patients,[62] but there are no data to suggest that estrogen replacement increases the risk of recurrence.

Many hysterectomies and oophorectomies are performed for pelvic pain; however, once the surgery is performed organs cannot be replaced should reduction of pain not be realized[63-64]. Almost 21–40% of women having a hysterectomy for chronic pelvic pain may continue to experience pain after the surgery.[65] The concept of "window into the future" is an important one when treating pain because of the subjective nature of the symptoms and the inability to restore normal pelvic anatomy should the surgery not result in pain control. Hence, the importance of a course of GnRH Agonist or other pseudo-menopause therapy can not be over emphasized prior to embarking on definitive surgery.

In women electing hysterectomy and bilateral oophorrecomy for definitive treatment of endometriosis, hormone replacement therapy (HRT) may be started immediately post-operative without fear of decreasing effectiveness of oophorectomy.[66]

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