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Management of Endometriosis Pain in 2019

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Abstract

Endometriosis is one of the most common gynecologic causes of chronic pelvic pain in women and affects 10% of reproductive aged women. The average age of diagnosis is 28, unfortunately, almost a decade of pain and symptoms pass before patients finally receive their diagnosis[1]. Endometriosis can be debilitating, impairs quality of life, and carry large financial burden for patients, their family, and society[2].

Keywords: Endometriosis; Menopausal; Dyspareunia; Laparoscopy

Abbreviations: NSAIDs: Nonsteroidal Anti-Inflammatory Drugs; DMPA: Depot Medroxyprogesterone; BMD: Acetate; Bone Mineral Densities; LNG-IUS: Levonorgestrel-Releasing Intrauterine Systems; BSO: Bilateral Salpingo-Oophorectomy; SERMs: Selective Estrogen Receptor Modulators; GnRH: Gonadotropin-Releasing Hormone

Endometriosis is a Chronic Disease

Endometriosis today should be approached as a chronic disease, similar to diabetes or hypertension. Therefore, patients with chronic pelvic pain due to endometriosis should be counseled with this chronicity in mind. It is essential to discuss the importance of extensively combined of medical and surgical options until menopause. Medical options that optimally manage endometriosis are incompatible with pregnancy, since they target the same hormones and tissue. As a result, clarification of reproductive expectations with your patient is an important first step. If their primary goal is fertility, then they are best served with pre-intervention conception planning with infertility specialists. However, if the goal is pain control then treatment should begin immediately.

Unless there is an acute pain exacerbation, or the patient is presenting after multiple prior failed medical options, the first line of therapy is medical management (Figure 1). The goal of medical therapy is to minimize pain and maximize patient quality of life. Medications that can be taken affordably long term, with minimal side effects should be recommended first. Only if medical management fails, should surgery be considered. Surgical goals are prioritized as definitively diagnose, stage, photograph, and, most importantly, excise endometriotic lesions to decrease the disease burden; similar to how oncology may approach a debulking surgery. After surgery, medical therapy is immediately restarted and continued until she opts to pursue pregnancy becomes menopausal.

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Medical Therapy

Many medical options on the market offer comparable results, particularly for classic cyclic pain associated with endometriosis. As a result, selection of the optimal medication should be based on patient age, preference, severity of disease suspected or known, desire for contraception, availability, cost, and side effect profiles [1]. Traditionally, nonsteroidal anti-inflammatory drugs (NSAIDs) and combined oral contraceptives (COC) are considered the first line therapy. The use of NSAIDs for endometriosis is a natural extension as they are quite effective in the management of routine dysmenorrhea3. However, a 2017 Cochrane review revealed that there is actually little data that NSAIDs are effective in treating pain due to endometriosis 4. (Table 1).

Treatment	Medication	Comments	Notable s/e
NSAIDs	Ibuprofen Naprosyn	Limited evidence of effectiveness in endo	Nausea, vomiting, GI irritation
Combined Oral Contraceptives (COC)	Monophasic estrogen-progestin*#	Traditional first line treatment Continuous use preferred Decrease Endometrioma size & prevent recurrence Not helpful in dyspareunia and nonmenstrual pain	
Progestins	**Better first line medication** Use continuously Decrease implant and endometrioma size		Erratic bleeding, weight gain, mood symptoms May have effects on lipid profile
	Medroxyprogesterone acetate 20-30 mg PO QD (MPA)	Similar effectiveness as Lupron in decreased pain, increased quality of life No maximum dose Safe for long term use	Minor effects on lipids
	Depo Provera 150 mg IM Q3 months, 104 SQ Q3 months*#	High patient satisfaction Equivalent to Lupron in decreased pain More side effects than other progestins	Irregular bleeding, bone loss, weight gain
	Norethindrone acetate 2.5 to 5.0 mg QD* (NETA)	Effective in dysmenorrhea, deep dyspareunia, nonmenstrual pain, dyschezia Best PO choice for rectovaginal and GI endo Higher patient satisfaction vs OCPs Good control of bleeding Can increase up to 15 mg Partly metabolized to estrogens → positive effects on bone metabolism	
	LNG-IUS Q5years (Q7yrs)#	Shown to improve pain in stage I-IV First line postop to prevent endometriosis Effective in decreasing dysmenorrhea & pelvic pain Good data to support use in rectovaginal/DIE	IUD discomfort , expulsion
	Etonogesterel releasing implant Q3 years (Q4yrs) #	Limited (promising) data that may decrease pain 3 years of ovarian suppression Similar pain and patient satisfaction to MPA	Erratic breakthrough bleeding
	lupron 3.75 mg IM Qm*	Only available IM	Lipid alterations, hot

Gonadotropin-Releasing Hormone Agonist	lupron 11.25 mg IM Q3m*	PO version currently in phase III trials Expensive Add-back therapy can be initiated immediately Not useful in postmenopausal women Treatment after surgery may decrease recurrence & pain	flashes, GU atrophy, depression, decreased libido Bone loss 13% after 6months if no add back Advise daily calcium 1,200 mg + vitamin D 800IU
GnRH Antagonist	Elagolix 150mg or 200mg PO QD	Decrease dysmenorrhea and nonmenstrual pelvic pain Expensive	Hot flashes, nausea, headache Hypoestrogenic effects that were similar to lupron, but lower magnitude
Selective progesterone receptor modulators	Mifepristone 50mg QD Ulipristal acetate 15 mg PO QOD	Experimental in endometriosis Ulipristal: liver function test monthly and stop if 2x normal.	Spotting, cramping, dizziness, headache, nausea Ulipristal: Reports of significant liver injury/failure; 4 requiring transplant
Androgen	Danazol 100–400 mg PO BID	Side effect profile make it unacceptable	weight gain, bloating, decreased breast size, ache, oily skin, hirsutism, headache, deepening of the voice, bone loss, hot flashes, and muscle cramps
Aromatase inhibitor	Anastrozol 1 mg PO QD Letrozole 2.5 mg QD	Primarily in research setting prior to menopause Effective in severe post-menopausal endo via blockade of extraovarian estrogen production	HA, nausea, diarrhea High bone loss with prolonged use Cannot be used as single agents in premenopausal women Must use with contraception to suppress follicular development
Add back therapy	Norethindrone acetate. 5 mg PO QD	Only FDA approved add back therapy Can be initiated immediately Fewer vasomotor symptoms Preserve bone mineral density	
	Conjugated estrogens 0.625 mg + norethindrone 5.0 mg PO QD	High dose of estrogen does not improve benefits	
	Combined OCPs	Not FDA approved for add back	

Table 1: Medical Management of Endometriosis
*FDA approved for endometriosis
#FDA approved for contraception

COC do effectively treat endometriosis symptoms in some patients. When prescribing COC utilize a monophasic pill, either cyclically or continuously. Both regimens are effective, but continuous COC have been shown to provide better pain control[5]. COC have been shown to decrease endometrioma sizes and improve dysmenorrhea, but they typically provide less relief for dyspareunia and the noncyclic pelvic pain associated with advanced endometriotic disease. There is no data to suggest that switching between different COC types is effective if the

patient is not optimally managed on one. Instead, consider switching to a new category of hormone therapy or proceeding with surgery.

While the efficacy of estrogen in COC's is limited, but the progesterone component is quite useful in the treatment of endometriosis. Progestin monotherapy is rapidly gaining traction as it leads to similar or improved pain reduction and improved dysmenorrhea (compared with COC) without the estrogenic side effects [1-6]. Furthermore, the progestin-only agents can be safely used in those with contraindications to estrogen.

Many endometriosis specialists have moved towards progestins as the new first line treatment in the medical management of endometriosis. Studies have demonstrated that with continuous use, patients have improved pain, higher amenorrhea rates, and decreased endometrioma size compared to COC. All progestins have been shown to be effective at treating endometriosis, including rings, IUDs and implants. The most commonly used of progesterone-only agents include medroxyprogesterone acetate (provera) and depot medroxyprogesterone acetate (DMPA). Provera is readily available, inexpensive, well tolerated, and moderately effective however the optimal dose has not been defined. DMPA has been shown to be as effective in pain reduction as Lupron in with fewer hypoestrogenic side effects [7]. DMPA has been shown to decrease pain but is associated with more irregular bleeding [8]. Additionally, DMPA causes concern regarding bone mineral densities (BMD). BMD associated with DMPA use appears to reverse after discontinuation and does not appear be a link to increased risk of osteoporotic fractures later in life [8,9].

Norethindrone acetate (NETA) has been shown to improve dysmenorrhea, deep dyspareunia, nonmenstrual pain, and dyschezia. NETA is the most effective oral choice for rectovaginal endometriosis and bowel endometriosis available. Studies comparing NETA to surgery at one year showed that those patients with early stage endometriosis did better than surgery, and that those with advanced disease using NETA had comparable results to surgery [10]. NETA is available in a 5 mg pill, however studies using the medication show efficacy with fewer side effects at a 2.5 mg/day dose for the majority of women [11]. If needed, the dose can be increased but consider monitoring lipid profiles for those in higher doses chronically. Consider NETA as an excellent first line medication due to its low cost, low side effect profile, and its ability to treat a wide spectrum of endometriosis effectively.

Levonorgestrel-releasing intrauterine systems (LNG-IUS) have been shown to improve pain in randomized controlled studies for all states of endometriosis and are similar to GnRH analogues to control pain. This makes the LNG-IUS an excellent choice as primary treatment of endometriosis and pelvic pain, in those patients who also wish to utilize a LARC for pregnancy prevention. Despite its local action, the LNG-IUS has strong data to support its use in rectovaginal endometriosis and deep infiltrating endometriosis with or without prior surgery [12].

The data on LNG-IUS on preventing and decreasing endometrioma size is smaller and conflicting. Since LNG-IUS does no suppress ovulation in most patients, it is likely may not able to suppress endometrioma recurrence as effective other medications [11]. Until further data is available, consider COC which has improved outcomes in preventing endometrioma recurrence documented. Other intrauterine systems (etonogestrel), have less robust data available but also show that it may decrease pain. A frequent complaint with progestin monotherapy (of any form) is breakthrough bleeding which can be relieved with a 7- to 14-day course of oral estrogen if no contraindications are present.

GnRH agonist (leuprolide) decreases the pituitary gonadotropins and prevents future synthesis while present. This depletion leads to a hypoestrogenic state and relief of endometriosis symptoms and possibly regression of endometriotic lesions, however Lupron causes many undesirable side effects. Lupron should not be used to diagnosis endometriosis, because the hypoestrogenic state and resulting amenorrhea will treat a variety of conditions causing pelvic pain, not just endometriosis. So, while Lupron is effective, it lacks specificity for the diagnosis of endometriosis. Also because of its mechanism of action, Lupron is not useful in postmenopausal women because they are already in a hypoestrogenic state.

Lupron is effective in treating in endometriosis and can decrease pain by 60-100%. Lupron is expensive and can have significant side effects. After only six months of use, bone loss in adults was noted to be upwards of 8% when add back therapy was not given [13]. Add-back therapy can be initiated immediately with no effect on worsening endometriosis symptoms [14]. NETA 5 mg has been FDA approved for use in conjunction with GnRH agonists. For women who do not tolerate the higher dose progestin add-back therapy, the combined estrogen (0.625mg) and 5mg NETA have been demonstrated to have improved side effects.

In this study increasing doses of estrogen did not improve upon symptom relief [13]. One concern often discussed about NETA are the estrogenic metabolites (ethyl estradiol) that is produced when it is metabolized. There are often concerns with prescribing estrogen to women with endometriosis due to concerns of exacerbating their disease. However, it is due to these estrogenic metabolites that likely makes NETA more effective than other progestins. These metabolites likely assist in bone loss prevention during treatment and add-back. Patients on Lupron should also be advised to take daily supplemental calcium 1,200 mg and vitamin D 800 international units.

In July 2018, the FDA approved the first new treatment for endometriosis to be released since leuprolide acetate in June 1999. Elagolix is a gonadotropin-releasing hormone (GnRH) receptor antagonist specifically FDA approved for the treatment of moderate to severe pain due to endometriosis. As an antagonist, it competes with GnRH for pituitary receptors; partial suppression is found at lower doses and full pituitary and ovarian hormone suppression can be found at larger doses [15]. In trials, elagolix was most frequently noted to cause hot flushes, headache, and nausea; however significant reductions in dysmenorrhea and pelvic pain were noted [16]. Additionally, elagolix was noted to have a negative impact on bone mineral density, increased lipid levels, and hot flashes [16]. Elagolix is contraindicated in women with known osteoporosis.

Other medications are available and on the market, but fall into the realm of theoretical but not practical for most general ObGyns. Danazol, frequently used in the 1980s, is effective due to its ability to cause endometrial tissue atrophy. However, the androgenic side effects (weight gain, acne, and hirsutism) are often unacceptable to many patients and can be irreversible [17]. Aromatase inhibitors (anastrozole, letrozole) suppress extraovarian estrogen production by preventing conversion of androgen into estrogen [18]. They are a promising treatment option in combination therapy with progestins, but its use is off label for the treatment of premenopausal endometriosis patients [14]. Also, aromatase inhibitors are often linked to myalgias and arthralgias with chronic use, therefore utility may be limited in endometriosis patients [19].

Selective progesterone antagonists are also being investigated, however neither mifepristone nor ulipristal acetate have been approved [20]. Mifepristone may have beneficial effects on dysmenorrhea and dyspareunia, but there is no dosing consensus [20]. Ulipristal acetate is currently under evaluation, however, reports of significant liver injury with some patients requiring liver transplant have marred its image. Selective estrogen receptor modulators (SERMs) like raloxifene have limited data available [21]. While it is comforting to know there are potential options on the horizon, but remember there are already good options currently available for endometriosis management.

Surgical Therapy

The decision to proceed to the operating room is always difficult with several influential factors weighing heavily. Consider taking to the operating room any patient who has failed medical management, has an intolerance or contraindication to medical therapy, has need for definitive diagnosis, or for immediate treatment of pain in acute settings. Another factor is patient autonomy and their desire to undergo surgical evaluation and management. It is important to counsel patients regarding the benefits, risks, potential complications, and limitations of surgical intervention, and that medical therapy should be utilized before and after for the best results.

Excision or Resection	Hysterectomy + Excision/Resection	Hysterectomy + BSO + Excision/Resection
Age?	**Age?**	**Age?**
Desires preserved fertility	Completed fertility	Stage 4 endometriosis
History of prior significant symptom relief after surgery	Contraindication to estrogen add back therapy	Refractory to medical management
Concern for other contributing etiologies of pain (muscle, bladder, bowel, etc.)	"Failed" medical management and has notable uterine pain on exam	Oophorectomy recommended for other reason (BRCA, Lynch, etc.)
Declines hysterectomy	Desire for possible future egg retrieval	Patient concern or request*
		? Response to Lupron

Table 2: Surgical Options.
* After thorough counselling regarding pros/cons of ovary removal

The decision on what surgery to perform is also multifactorial (Table 2). Historically, women with endometriosis have been managed definitively with an abdominal hysterectomy and bilateral salpingo-oophorectomy. This was often offered as treatment in spite of their reproductive goals. In 2019, however, as our medical and surgical options are improving, the necessity of this drastic and morbid surgery is lessening. As we have reviewed, there are many options for medical management, and the goal should be to initiate medical therapy. Surgery should be used as a diagnostic tool and then as a tool for symptom management.

With appropriate suppression prior to surgery, complete surgical optimization and removal of all visible endometriosis (Figure 1 and 2), followed by suppression (aka: the "suppression sandwich"), postoperatively,

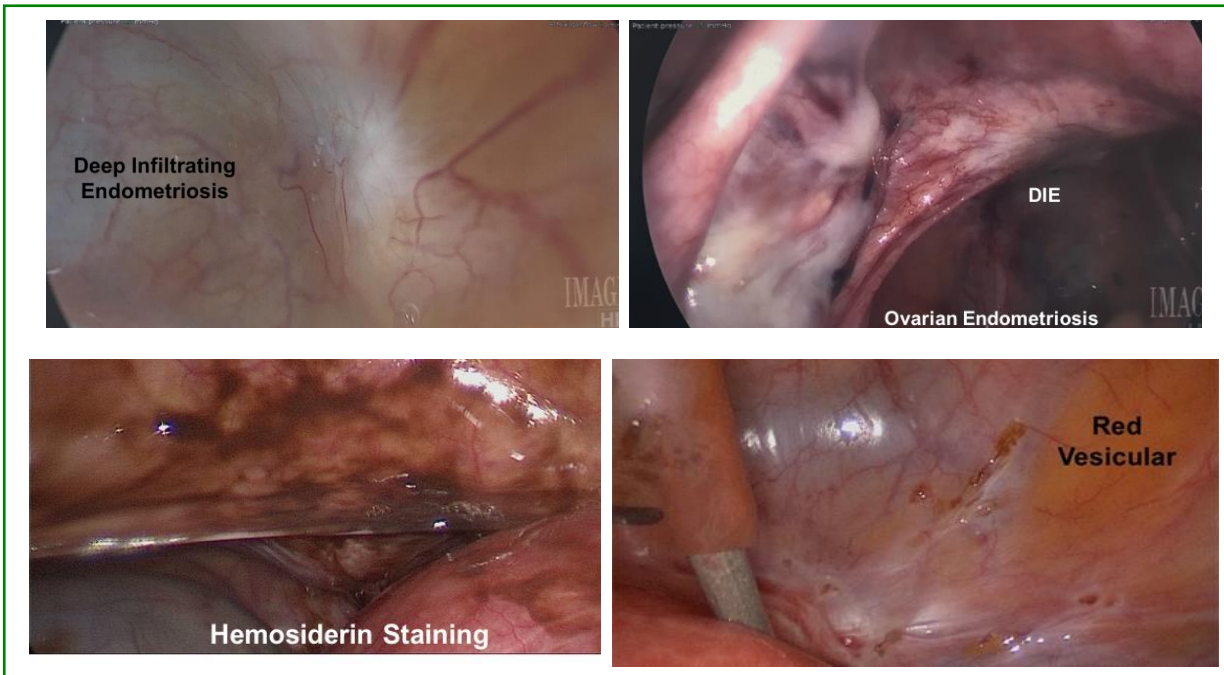

Figure 1: Types of Endometriosis.

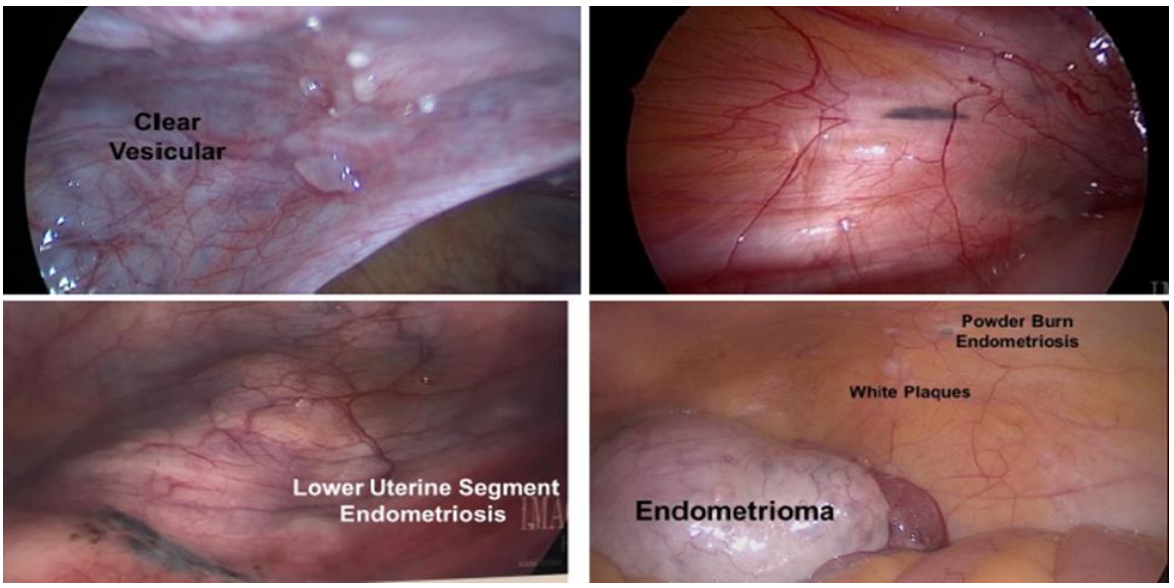

Figure 2: Types of Endometrosis.

Many patient symptoms can be managed for years until their reproductive goals have been met (Figure 3). When planning for surgical optimization, the gold standard approach for conservative treatment of endometriosis is laparoscopy. The goals for conservative surgery are to obtain a diagnosis, restore anatomy, treat visible disease, and prevent adhesions. If surgery findings suggest advanced endometriosis or deep infiltrating endometriosis, then it allows for appropriate treatment planning postoperatively.

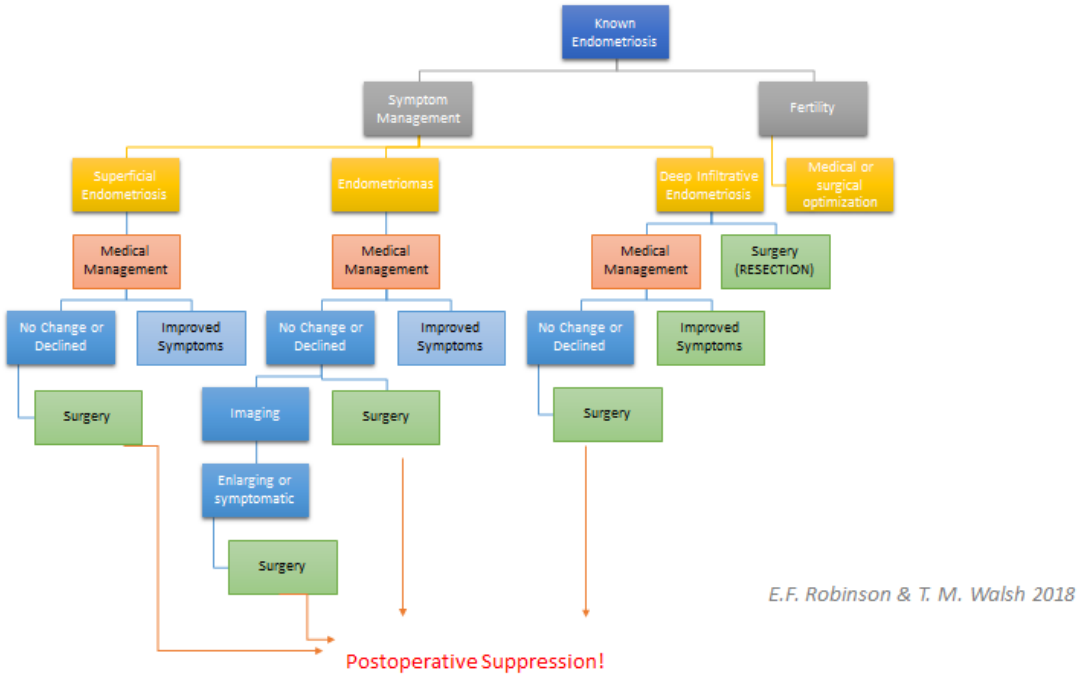

Figure 3: Endometriosis Management Algorithm

When performing conservative surgical management, similar to medical management, there is evidence that doing something (excision or ablation) will have better patient outcomes than performing just a diagnostic laparoscopy. At 6 months, operative laparoscopy is 65% effective in reducing pain, as compared with a 22% rate of pain reduction associated with diagnostic laparoscopy alone. A systematic review from 2017 looked at the optimal surgical approach for treatment of endometriosis, and though the trend favored excision, there was no statistical difference in the pain scores when comparing ablation to excision [22]. For many endometriosis surgeons, it's often commented that there is likely no difference between excision and ablation for early or superficial disease if all disease is treated. It is important to note that great care should be taken with ablation as endometriosis does frequently localize near vital structures (bladder, bowel, nerves, ureter, and vessels) that can be damaged by the lateral spread of energy.

For advanced stage disease (III, IV, and deep infiltrative), excision is preferred. This is initiated via a technique referred to as peritoneal stripping. Peritoneal stripping aims to remove all visible and palpable endometriosis nodules, lyse adhesions, and restore normal anatomy (Figure 4). When conservative surgery is performed, without postoperative medical therapy, pain symptoms have a high recurrence rate of up to 50% at 5 years [1]. Again, since hormonal management is required long-term careful consideration of medications that can be utilized long term by your patient (Table 1).

Endometriomas

While endometriomas can be difficult to address, we do know that they rarely spontaneously resolve. Medical management of endometrioma can result in stabilization or small decrease in cyst size, but surgical therapy is required when endometriomas remain symptomatic or large.

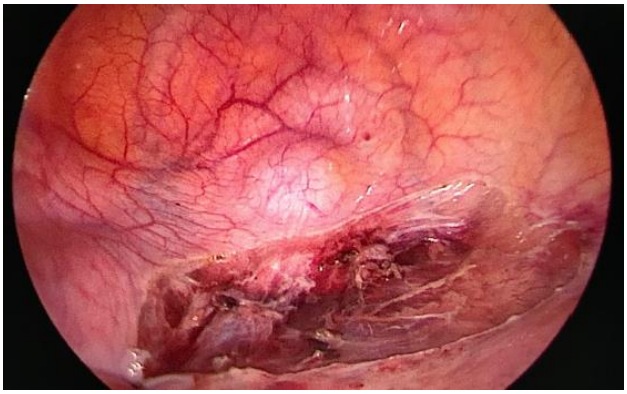

Figure 4: Peritoneal Stripping.

It is not clear what role endometriomas play with regards to fertility. There is some data to suggest removal of endometriomas in women who are subfertile may increase spontaneous pregnancy rate [23]. Interestingly, the presence of endometriomas do not seem to affect ovarian function, however, surgical resection of the endometrioma is associated with a decrease in ovarian reserve [24]. If the patient is pursuing fertility services, the recommendation is to leave the endometriomas, allow for stimulation, retrieval, and fertility treatments by an REI.

Once fertility treatments are completed, or if the patient is severely symptomatic, surgery is the next step. Surgical management of endometriomas should be in the form of cystectomy with minimal use of energy for hemostasis. Cystectomy is more likely to relieve symptoms and prevent rapid recurrence than cystotomy with drainage or ablative techniques. Surgery with drainage of cyst alone is associated with a high recurrence rate (80-100% *by* 6 months) and a high reoperation rate; both which are associated with decrease in ovarian volume and adverse fertility outcomes [1]. When appropriate postoperative medical treatment is initiated, the endometrioma recurrence rate declines to 3-11% at two years and 6% at five years.

Ovarian Conservation with Hysterectomy?

Historically, total hysterectomy with bilateral salpingo-oophorectomy (BSO) was considered the definitive management for women with endometriosis and severe pain. While hysterectomy can often help with dysmenorrhea and other uterine sources of pain, oophorectomy has not been shown to consistently reduce the risk of recurrent pelvic pain even among women with endometriosis. There is evidence to support that younger women (aged less than 40) may not benefit from BSO at the time of hysterectomy as it does not decrease their reoperation rates and they have prematurely entered surgical menopause. For women over the age of 40, the risks and benefits may be a more appropriate balance in decreasing reoperation rates as they near menopausal age. Regardless, all patients should participate in an extensive preoperative discussion with their surgeon. A review of ACOG recommendations, the risk of reoperation after ovarian conservation, the potential need for postoperative hormone replacement, and the irreversible consequences of oophorectomy should be discussed. In reality, a minimally invasive oophorectomy can be performed as an outpatient procedure for the majority of women at a later date if indicated.

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