

Endometriosis - An Update

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Summary:

Endometriosis is a common and important health problem of women. The prevalence of endometriosis is difficult to determine. Diagnosis is often difficult and delayed due to close similarity of symptoms of endometriosis with other gynecological disorder. Optimum treatment involves a combination of medical and surgical treatments tailored to the patient's needs and response.

The objective of the study is to discuss the current updates on diagnosis, treatment and the optimal role of different options in the treatment of endometriosis. The article reviews different medical journals, medline and internet to get the

relevant information. The study results showed that both medical and surgical treatments are almost equally effective in pain management there is no evidence that medical treatment improves fertility. Surgical treatment is associated with small but significant improvement in live birth rate. Newer non hormonal drugs are more selective with less metabolic side effects. Surgical treatment is invasive procedure and repeated surgery is associated with major complication.

Medical treatment is considered more effective in the long term management of endometriosis.

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Introduction:

Endometriosis is a chronic and recurrent disease characterized by the presence and proliferation of functional endometrial glands and stroma outside the uterine cavity. Around 10% of women of reproductive age are affected by endometriosis, suffer from chronic pelvic pain and contribute to infertility¹. Endometriosis not only lowers the quality of life of the affected women; it jeopardizes her conjugal life, hamper wellbeing of other members of the family and ultimately the society is also affected. The original three theories of histogenesis of endometriosis fail to explain all the criteria of histogenesis. According to serosal cell metaplasia theory endometriosis should occur in men also. Few rare case of endometriosis in male has been reported^{2, 3}. The recent molecular explanation for Sampson's theory states that aberrant production of aromatase converts the precursor of steroids to estrogen in endometriotic tissue that plays a key role in the path physiology of endometriosis⁴.

Endometriosis run in families. The mode of inheritance is probably polygenic and multi factorial. Chromosome no 10 q26^{5, 6} is thought to carry the involved gene. There is some defect in immune response to tissue injury in women with endometriosis that fail to remove refluxed menstrual debris from the extra uterine site. The scavenger activity of peritoneal macrophages is reduced⁷ with abnormal T-cell-mediated cytotoxicity,^{8, 9} natural-killer-cell activity,¹⁰ B-cell functions and complement deposition. They suffer from different autoimmune diseases, allergic reactions and certain toxins^{11,12}. Growth factors may also have some role.^{13, 14}. Another area of research is the search for endometriosis markers. CA 125 is elevated in patient with endometriosis.¹⁵

Clinical findings:

Endometriosis is associated with a wide variety of symptoms ranging from mild dysmenorrheal to incapacitating pain. Pelvic pain is usually cyclical and become severe as the disease advances.¹⁶ Pain of endometriosis has a diverse presentation causing dysmenorrhea, deep dyspareunia, constant pelvic pain or a low sacral backache. One of the characteristics of the disease is that the symptoms do not correlate with the amount of the disease. There are women with minimal disease but with lot of symptoms. On the other hand there are women who have lot of disease with minimal symptoms.¹⁷

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Infertility is another common association of the disease. It's incidence among infertile women according to one study is 14%¹⁸. There is evidence of impaired oocyte development, embryogenesis or implantation in mild degree endometriosis¹⁹. Many cases of endometriosis suffer from dysfunctional uterine type of bleeding²⁰. Endometriosis is often confused with pelvic inflammatory disease, irritable bowel syndrome and pelvic tumor which often causes delayed diagnosis and require surgical evaluation.

Diagnosis AMD Staging

In current clinical practice, laparoscopy is required for a definitive diagnosis of endometriosis. Histological evaluation is essential when the diagnosis is not obvious on visual inspection at surgery. When addressing whether or not to perform a laparoscopy on a women presenting on a complain of infertility, one should consider both the likelihood of diagnosis of endometriosis as well as potential benefit of treatment. A history and physical examination can yield a number of significant findings suggestive of endometriosis including: cyclic or chronic pelvic pain dysmenorrhea, dyspareunia, a fixed retroverted uterus, an adnexal mass, and uterosacral ligament nodularity, thickening or tenderness. Pelvic ultra sound can help the clinician to establish a presumptive diagnosis of an endometrioma but cannot detect peritoneal implants of disease.

A laparoscopic diagnosis of asymptomatic endometriosis can sometimes be made. However, laparoscopic confirmation of asymptomatic endometriosis is almost always limited to minimal or mild disease. The therapeutic benefit of laparoscopy to increase fecundity in a woman with mild disease is minimal. The combination of these factors renders laparoscopy of asymptomatic women with infertility, simply to rule out or confirm disease, unwarranted^{20,21}.

Endometriosis is a heterogeneous disease with typical and atypical peritoneal lesions ranging from a single 1mm peritoneal implant to less than or equal to 10 cm endometriosis with cul-de-sac obliterated. Thus a staging system has been proposed for better understanding the extent of disease and standardization and comparisons of outcomes for clinical trials. The American society of Reproductive Medicine classification system for endometriosis (ASRM 1996) is the most widely accepted staging system²². No staging system correlates

well with the chance of conception following therapy. This poor predictive ability is related to the arbitrary assignment of point scores for the observed pathology and the arbitrary cut-off points chosen to establish the stage of disease. The description of the morphologic subtype of disease or other biological markers may be included with The ASRM 1996 classification system.²³ A better understanding of the patho-physiology of endometriosis-associated infertility may help to develop a more accurate staging system.

Treatment options:

Medical treatment is usually considered as the first line of treatment. Treatment is often individualized and is tailored depending on patient's age, desire for future fertility, severity of symptoms and the stage of disease. Endometriosis is a disease of pain. Empirical treatment of pain is offered to suspected cases of endometriosis without a definitive diagnosis. It includes counseling, adequate analgesia, progestogens, the combined oral contraceptives (COC), gonadotropin releasing hormone (GnRH) agonists and antagonists, danazol, nutritional therapy and most recently aromatase inhibitors. All of them are appropriate for pain management and where there is no desire for immediate fertility²⁴.

The Hormones can effectively control pain and reduces anatomical extent of the disease. Only they differ in side effect and cost profile. Symptoms recur after discontinuing therapy. There is no improvement in infertility by medical management.

Oral contraceptive pills (OCPs): OCPs are considered as number one choice for patients having minimal or mild symptoms. It can be given cyclically and continuously for 2 years²⁵.

Progestin alone or combined with estrogen are used frequently for long term management of endometriosis associated pain²⁶. Progestins inhibit angiogenesis which is required for maintenance of endometriotic implants²⁷. They are available in multiple delivery forms, convenient in dose and have less impact on bone mineral density (BMD).

Medroxy progesterone acetate is the most popularly prescribed progesterone that causes relief of pain ranging from 70% to 100%. It is as effective as danazol and is better than placebo²⁷.

The levonorgestrel intra-uterine system (LNG IUS): it is a newer non daily hormonal preparation²⁸. It is

convenient in symptom control for over 3 years. It may have the potential to be a long term treatment option for endometriosis.

Danazol is 19 nor testosterone derivative. Numerous clinical trials have proved that danazol is effective in regressing endometriosis implants with relief of pain²⁹. Women with all stages of disease showed no difference in improving fertility between danazol and placebo group³⁰. Danazol was the gold standard of treatment of endometriosis. The treatment course is limited for six months for its androgenic side effects of which male type of hair growth and voice change may be irreversible³⁰. Women need effective contraception during the course of treatment.

Gonadotropin releasing hormone agonists: Recently this drug has gained popularity in the medical management of endometriosis³¹. It causes medical menopause by down-regulating hypothalamic pituitary GnRH receptors. Mafarelin, buserelin, histrelin, goserelin, triptorelin and leuprolide are the available analogues in use. They are associated with many hypo estrogenic side effects. The most significant one is loss of bone mineral density [BMD]. There is evidence of 3.2% reduction of BMD in lumbar spine [BMD] after six months and 6.3% after 12 months of continuous treatment¹⁸. The treatment course is restricted to six months. The use of "add back" regimen with [GnRH] has prolonged the duration of therapy for up to two years³². Norethindrone acetate 5 mg daily, low-dose estradiol plus a progestin, a progestin plus bisphosphonate are used in the regimens.

The newer medical treatment modalities: These drugs are more selective and acts on estrogen dependent growth of endometrial lesions. Aromatase inhibitors, selective estrogen receptor modulators (SERMs) Progesterone receptors modulators (SPRMS) are newer drugs with selective mode of action. They are still under ongoing research.

Aromatase inhibitors: aromatase P450 is an important enzyme for estrogen biosynthesis. It acts as catalyst in the conversion of androstenedione and testosterone to estrone and estradiol. This enzyme is present in a very high level in the endometriotic tissue. Aromatase inhibitors inhibit the growth of endometriotic implants by suppressing this enzyme³³. In one study, aromatase inhibitors letrozole 2.5mg per day with calcium and

vitamin D for six months caused marked reduction of laparoscopic visible lesion and significant reduction of pelvic pain with no changes in BMD³⁴.

Anti-estrogens: Non-steroidal anti-estrogen can act as either estrogen agonist or antagonists. It acts by binding with estrogen receptors (ERs) and depending on the target tissue, they are known as selective estrogen receptor modulators (SERMs). In the treatment of endometriosis, SERMs have estrogen antagonist activity on the endometrium and agonist activity on bone and circulating lipoproteins³⁵.

Progesterone receptors modulators (SPRMS): The SPRMs bind to progesterone receptors and can act as either agonists or antagonists of progesterone activity. Their activities depend on target tissue, dose of the drug and presence or absence of progesterone³⁶. They can suppress endometrial proliferation selectively with no side effects of systemic estrogen deprivation. J867, J956, J912 and J1042 are some of the SPRMS. J867 was found promising in preliminary studies. At present there are insufficient data to evaluate the efficacy of these drugs. These drugs are under clinical trials in animals. More research is needed to assess the role of these agents in the treatment of endometriosis.

Surgical treatment:

Surgery remains a major treatment modality for endometriosis. Laparoscopy is the gold standard diagnostic aid for endometriosis. It provides better visualization and more complete excision than laparotomy.

There are differences in opinion whether to strip or destroy the wall of ovarian endometrioma and the extent of surgery in recto vaginal disease. Excisional treatment is more effective and successful^{54,55} with 5 years cure rate of 81%^{37,38}. Hysterectomy and bilateral salpingo-oophorectomy is considered as the most definitive surgery. 39 It results in satisfactory pain relief and less chance of repeat surgery compared to hysterectomy with preservation of one or both ovaries⁴⁰.

In rectovaginal endometriosis hysterectomy with removal of part of lower bowel causes considerable pain relief and improves quality of life⁴¹. In chronic pelvic pain the nerves from the uterus to the brain are cut. They have limited value in pain relief⁴². Surgery results in pain relief in 80 % of women who fails to respond to hormonal treatments⁴³. Surgery for deep lesions is

difficult, complex and may lead to major complications⁴⁴. No treatment is offered to the asymptomatic cases even deeply infiltrating rectovaginal endometriosis^{40, 41}.

Ovarian endometriosis: Treatment depends mostly on the size and type of lesion. Superficial implants are destroyed by coagulation or vaporization. Cysts larger than 3cm gives better results with excision than drainage and coagulation⁴⁵ There is a four fold increase chance of ovarian carcinoma in patients with endometriosis^{70, 71}. Cancer may develop directly from the implants and even after bilateral salpingo-oophorectomy⁷². The histological subtypes are usually endometrioid and clear cell carcinoma⁴⁶.

Combination medical and surgical therapy:

It consists of either preoperative or postoperative medical therapy. There is no evidence in the literature that combined medical surgical treatment significantly enhances fertility. Preoperative therapy reduces pelvic vascularity and the size of the endometriotic implants which reduces per operative blood loss and decreases the amount of surgical resection needed. Postoperative medical therapy is planned for eradicating residual endometriotic implants with extensive disease where resection of all endometriotic implants is impossible. Postoperative hormonal therapy is thought to treat microscopic disease. However fertility is not enhanced by any means.

Treatment of endometriosis associated infertility. Following are recommended treatment options

Super ovulation and intrauterine insemination

Different studies have been conducted to assess the success with superovulation (SO) and intrauterine insemination (IUI) in the treatment of endometriosis-associated infertility. In a cross-over RCT among patients with unexplained infertility or surgically corrected endometriosis, the pregnancy rate per cycle was significantly higher with four cycles of clomiphene citrate/IUI than with four cycle of timed intercourse (9.5% versus 3.3 % respectively)⁴⁷. A randomized trial among 49 women with stage I/II endometriosis and infertility compared three cycles of gonadotropin/IUI with six months of expectant management⁴⁸. The pregnancy rate per cycle was 15% in the gonadotropin/IUI group and 4.5% in the untreated group (P<0.005).

Another study report increased fecundity with gonadotropin therapy compared to no treatment (7.3% vs 2.8% respectively) in women with infertility and minimal or mild endometriosis⁴⁹.

The clinical pregnancy rate using SO/IUI shortly after laparoscopic excision of minimal or mild endometriosis was comparable in women with unexplained infertility and some of 'untreated endometriosis. The per cycle pregnancy rates in women with minimal endometriosis, mild endometriosis, or unexplained infertility were 21%, 18.9% and 20.5% respectively. Cumulative live-birth rates following 4 cycles among the three groups were 70.2%, 68.2%, and 66.5% respectively⁵⁰. Thus SO/IUI is a considerable treatment option for women who have had a surgical diagnosis and treatment of stage I or II endometriosis as an alternative to in vitro fertilization (IVF) or further surgical therapy.

Several randomized clinical trials (RCTs) have shown that progestins or gonadotrophin releasing hormone (GnRH) agonists are not effective treatment for infertility associated with minimal to mild endometriosis.⁵¹ A reviews of 13 RCTs among 800 infertile women, hormonal treatment does not improve the fecundity of the women with stage I/II endometriosis. It is also not effective in severe disease. Ablation of endometriotic lesions and adhesiolysis improves fertility in mild and minimal lesions. In women with stage III/IV endometriosis who have no known infertility factors, conservative surgical treatment with laparoscopy or laparotomy may increase fertility⁵². With respect to severe endometriosis, a nonrandomized study demonstrated that the cumulative pregnancy rates in 216 infertile patients followed for up to two years after laparoscopy or laparotomy were 49% and 63% respectively⁵³. After the first infertility operation, additional surgery rarely increase fecundability and these patients are better served by assisted reproductive technology (ART)⁵⁴.

Assisted reproductive technique (ART):

The techniques are offered in selective cases. Elderly infertile women with endometriosis who do not respond to other therapies are treated with ovulation induction, intra uterine insemination (IUI) or in vitro fertilization (IVF)/Intracytoplasmic sperm injection (ICSI) technique. The pregnancy rate is higher with controlled ovarian hyper-stimulation for three cycled (15%) than

among untreated women (4.5%) (77)⁵² the results of IVF/ ICSI or gamet intra fallopian transfer (GIFT) is hopeful among infertile women with endometriosis (78)^{54,55}.

Intracytoplasmic sperm injection (ICSI) is a new technique to treat male infertility problems like Azospermia, Aspermia but have limited success.

Hormone replacement therapy: Hormone replacement therapy (HRT) is recommended for young women after bilateral oophorectomy with a small risk of recurrent disease⁴⁸.

Conclusion:

Endometriosis is an extremely complex medical disorder and treatment is also complicated. Both GnRH and danazol are of limited use for their substantial metabolic side effects. Progestins alone or combined with estrogen are effective for long term management of pain in women who do not desire pregnancy. The non daily hormonal delivery option (transdermal, intra vaginal and SC injectable) are more convenient and consistent in use for many women. DMPA-SC 104 reduces pain effectively and it has less impact on BMD. Aromatase inhibitors, SERMS and SPERMS are unique as their activities are target organ specific but they are in early stages of development. More research needs to be conducted to ameliorate the associated pain, infertility, to develop non invasive diagnostic tests and to find out the genetic involvement of the disease, and to find out the most appropriate treatment option.

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