Medical Treatment of Endometriosis

Hong-Yuan Huang, MD

Endometriosis is a common, benign and chronic gynecological disorder. It is also an estrogen-dependent disorder that can result in substantial morbidity, including pelvic pain, progressive dysmenorrhea, dyspareunia, infertility and repeat surgeries. Endometriosis is often treated surgically upon diagnosis but with a higher rate of recurrence, suggesting that a combination of surgical and medical management might provide better outcomes. The primary goal of medical treatment for endometriosis is to halt the growth and activity of endometriosis lesions. The most widely utilized medical treatment for endometriosis involves use of gonadotropin-releasing hormone (GnRH) agonists and oral contraceptives. Conventional agents also include androgen derivates and progestins. Due to the chronic nature of this disease, long-term or repeated courses of medication may be required to control its related symptoms. Increasing knowledge about the pathogenesis of endometriosis at the cellular and molecular levels may give us the opportunity to use new, specific agents for treatment, including aromatase inhibitors, progesterone antagonists, selective progesterone receptor modulators, GnRH antagonists, intrauterine releasing systems with progestin and new pharmaceutical agents affecting inflammation, angiogenesis, and matrix metalloproteinase activity. Many of these promising new agents may prevent or inhibit the development of endometriosis. Further clinical trials may determine if these new therapies are superior to current medical treatment strategies for endometriosis. *(Chang Gung Med J 2008;31:431-40)*

Dr. Hong-Yuan Huang

Key words: endometriosis, gonadotropin-releasing hormone, progestin, aromatase inhibitor

Endometriosis is a common, benign and chronic gynecological disorder. It is also an estrogen-dependent disorder that can result in substantial morbidity, including pelvic pain, infertility and multiple operations. It is characterized by the presence of uterine ectopic endometrial tissue outside of the uterine cavity-mainly on the pelvic peritoneum, but also on the ovaries and in the recto-vaginal septum, and more rarely in the pericardium, pleura, and urinary tract. The prevalence of pelvic endometriosis approaches 6-10% in the general female population. The frequency of disease is increased to 35-50% in women with pelvic pain and infertility.[1-4] Despite its high prevalence and its recognition for most of the past century as an important cause of infertility and pelvic pain, its underlying mechanisms and patho-

From the Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Taipei, Chang Gung University College of Medicine, Taoyuan, Taiwan.
Received: Jun. 29, 2007; Accepted: Jan. 3, 2008
Correspondence to: Dr. Hong-Yuan Huang, Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital. No. 5, Fusing St., Gueishan Township, Taoyuan County 333, Taiwan (R.O.C.) Tel.: 886-3-3281200 ext. 8251; Fax: 886-3-3288252;
E-mail: hongyuan@cgmh.org.tw

physiology still are poorly understood. No single theory can explain the pathophysiology of all endometriosis.[5]

The standard diagnosis of endometriosis is surgical assessment by laparoscopy or laparotomy. A scoring system has been developed and revised to assess the extent of disease.[6,7] For women with pain and with extensive adhesions, conservative surgery commonly provides temporary relief, although symptoms may occur again in most women within two years and further surgery is needed in these cases.[8,9] Because endometriosis is an estrogen-dependent disease, standard medical treatments aim at inducing hypoestrogenism and then inducing atrophy of ectopic endometrial implants. Medical hormone therapies historically have included oral contraceptives, progestins, and gonadotropin releasing hormone (GnRH) analogues, as well as androgen derivatives, and these have all been used successfully in the treatment of endometriosis.[10-13] All of these treatment modalities can be used only for a limited time owing to unacceptable side effects, including climacteric syndrome and loss of bone density. In addition, almost all of these treatment modalities fail to treat endometriosis-associated chronic pelvic pain and these drugs cannot cure the disease. At the present time, GnRH analogues are the most common medical therapy for endometriosis.[14,15] They dramatically reduce the estrogenic pattern in patients with endometriosis but the effects of GnRH analogues are temporary because endometriosis foci cause problems again at the resumption of menstruation after cessation of treatment. However, our understanding of the pathogenesis of endometriosis at the cellular and molecular levels has improved significantly in recent years. Novel therapeutic strategies may improve our ability to eliminate endometriosis lesions which are already present and to prevent the recurrence of endometriosis and the multiple operations after initial surgical treatment.[16] This review focuses on standard medical treatment with conventional and new modalities in the medical treatment of endometriosis and its related clinical symptoms (Table 1).

Conventional medical treatments

The primary goal of medical treatment for endometriosis is to halt the growth and activity of endometriosis lesions. Conventional medications used to achieve this goal include androgen derivates, progestogens, oral contraceptive pills and GnRH agonists.[17-19] Conventional treatment approaches for the medical management of endometriosis usually are carried out in patients with suspected endometriosis, in those with a confirmed diagnosis of endometriosis, in those who have had surgical

Table 1. Summary of Medical Treatments for Endometriosis

Agents	Mechanism	Effect	References
Conventional medical treatments			
Oral contraceptives	decidualization and subsequent atrophy of endometrial tissue	Symptom relief	17, 21
GnRH agonists	down -regulation of the pituitary-ovary axis and hypoestrogenism	Symptom relief and decreased disease	41
Androgens	hyperandrogenism, inhibit steroidogenesis	Symptom relief	26
Aromatase inhibitors	inhibit estrogen synthesis	Symptom relief	53, 54
GnRH antagonists	GnRH receptor blockade	Decreased disease	59
Progesterone antagonists	anti-progesterone	Decreased disease	66, 67
Selective progesterone receptor modulators	suppress estrogen-dependent endometrial growth	Symptom relief	71
Levonorgestrel-releasing intrauterine system	decidualization and subsequent atrophy of endometrial tissue	Symptom relief	74, 76

treatment of endometriosis and in those who need long-term management.

The most widely utilized hormonal treatments for endometriosis are GnRH agonists, oral contraceptives and the androgen, danazol. The majority of evidence in support of medical therapy for endometriosis is largely observational, with the exception of studies of GnRH agonists, danazol, and a few progestins.[20]

The advantage of an oral contraceptive over other hormonal treatments is that it can be taken indefinitely. An earlier study demonstrated that oral contraceptives were more effective in treating dysmenorrhea than GnRH agonists in fifty-seven patients with endometriosis. At the end of the six month follow-up, these patients did report a reduction in dysmenorrhea.[17] A further randomized study of ninety patients with recurrent moderate or severe pelvic pain after conservative surgery for symptomatic endometriosis demonstrated that oral contraceptives had the same efficacy and safety as cyproterone acetate in the treatment of endometriosis-associated recurrent pelvic pain.[21] According to an intention-to-treat analysis, 73% of patients (33 of 45) in the cyproterone acetate group and 67% (30 of 45) in the oral contraceptive group were satisfied with the treatment received in this study. Due to the chronic nature of the disease, long-term or repeated courses of medication may be required to control related symptoms. If oral contraceptives could be shown to be at least as effective as danazol or GnRH agonists, treatment options for long-term management of the disease could be broadened.[20,22]

Androgens can induce a hyperandrogenic state and induce atrophy of the endometrium, which is the rationale for their use in the treatment of endometriosis. Danazol, a synthetic isoxazole derivative chemically related to 17α-ethinyltestosterone, acts to increase the concentration of free testosterone by binding to sex-hormone-binding globulin and inhibits luteinizing hormone (LH) surge and steroid hormone production from the ovaries, resulting in a hypoestrogenic state.[23] All of this contributes to an inhibition of eutopic and ectopic endometrial growth. Multiple nonrandomized trials showed that the use of danazol resulted in an improvement in pain associated with endometriosis, in 66% to 100% of the women evaluated.[24-26] Common side effects related to hyperandrogenism which distress patients include hirsutism, acne, and a raspy voice. The majority of these patients refuse to be treated with danazol because of its potential androgenic side effects.[27] Alternate routes of danazol administration are under investigation.[28-30]

Many clinical trials have also compared the efficacy of danazol with that of the GnRH agonists. Both danazol and GnRH agonists showed the same efficacy in reducing both the growth of endometriotic implants and endometriosis-related symptoms during the treatment phases of the trial.[31-33] The obvious difference between them has been the profile of the side effects: the agonist has side effects associated more with a hypoestrogenic state and danazol more with an androgenic state, including weight gain, breast atrophy, hot flashes, and hirsutism.[34]

The role of GnRH agonists in reproductive medicine as well as in the treatment of prostate cancer, precocious puberty, endometriosis, and uterine fibroids has been fully demonstrated.[35-38] GnRH when administered in a pulsatile fashion binds to the pituitary receptors and activates the gonadotrophs to both synthesize and release LH and follicle stimulating hormone (FSH). Paradoxically, GnRH agonists are modified forms of GnRH that bind to receptors in the pituitary, but have a longer half life than native GnRH and thereby result in down regulation of the pituitary-ovarian axis and hypoestrogenism.[39]

GnRH agonists can be administered via a calibrated nasal spray, or by injection of either a short-acting formulation daily or of a depot formulation every one to three months. Side effects include hot flashes, vaginal dryness, decreased libido, mood swings, headache, and bone mineral depletion.[40] A long-term follow-up study of patients treated with a GnRH agonist alone for six months revealed a 53% recurrence of disease/symptoms two years after treatment.[41]

Aromatase inhibitors

It is well known that endometriosis is an estrogen-dependent disease and that this disorder tends to regress after estrogen deficiency. According to the two-cell two-gonadotropin theory, LH is capable of stimulating androgen substrate production from theca cells, to be transformed into estrogen by FSH-stimulated aromatase activity in granulose cells.[42] In the human, aromatase activity is expressed in several types of cells in the reproductive system including

the ovarian granulosa cell, the placental syncytiotrophoblasts and the testicular Leydig cells.[43] Aromatase is the enzyme that represents the critical step in estrogen biosynthesis. It catalyzes the conversion of C19 steroids to estrogens (estrone and estradiol).[44] Therefore, there are no important downstream enzymes to be affected, with the result that aromatase is an excellent target for inhibition of estradiol synthesis. In addition, because estrogen is needed to stimulate ectopic endometriotic tissues in patients with endometriosis and the because of the in situ presence of aromatase in these tissues, blockage of aromatase activity in these endometriotic sites with an aromatase inhibitor is a rational approach to medical treatment of endometriosis.[45,46]

The aromatase inhibitors are classified into type I and type II inhibitors. Both types of inhibitors compete for binding to the active site. Enzyme activity is then permanently blocked due to an unbreakable bond between the inhibitor and enzyme protein.[47-49] Several potent and selective third-generation aromatase inhibitors are available; of these, anastrozole and letrozole have substantial advantages over earlier agents in terms of efficacy and tolerability.[50] Although these agents have been widely used to treat postmenopausal or anovulatory patients with breast cancer, clinical experience with aromatase inhibitors in women with endometriosis is still limited.[51] A nonrandomized pilot study demonstrated that a combination of letrozole (2.5 mg/day) and norethindrone acetate for 6 months is effective in both reducing laparoscopically visible endometriotic lesions and decreasing pelvic pain scores.[52] In another representative study, two premenopausal sisters (24 and 26 years old) were diagnosed with endometriosis by laparoscopy and failed to respond to conventional treatment including oral contraceptives and GnRH analogues. An aromatase inhibitor (anastrozole 1 mg/day) was given with progestin (200 mg/day) for 6 months. The treatment resulted in a rapid progressive reduction in symptoms with the maintenance of remission of symptoms and absence of endometriotic lesions for more than two years after treatment in both cases. Pregnancy was achieved in both cases after two years. Side effects were minimal and well tolerated by both patients.[53] Recently, a prospective, randomized trial showed that 6 months of treatment with anastrozole (1 mg/day) and goserelin compared with goserelin alone increased the pain-free interval and decreased symptom recurrence rates in patients after surgery for severe endometriosis. Interestingly, the authors suggested that the efficacy of the protocol might be the result of the fact that goserelin inhibits ovarian steroidogenesis and anastrozole inhibits the consequences of peripheral aromatization and aberrant expression of aromatase in the endometriotic foci.[54]

In conclusion, patients with endometriosis who do not respond to existing treatments appear to obtain significant pain relief with aromatase inhibitors. Regimens which include combinations of an aromatase inhibitor with a progestin or oral contraceptive will probably become more popular than combinations of an aromatase inhibitor with a GnRH analogue because the former are cheaper with fewer side effects, and may be administered long term or for repeated courses.[55]

GnRH antagonists

Selective blockade of gonadotropin secretion and suppression of ovarian steroid production have previously been achieved by down - regulation of the pituitary gland to continuously administer by giving long-acting GnRH agonists. Recently, GnRH antagonists that immediately block GnRH effects have been developed for clinical use in endometriosis, leiomyoma, and breast cancer in women, benign prostate hypertrophy and prostate carcinoma in men, and precocious puberty in children.[56] The antagonistic properties of GnRH exert their effect by competing with endogenous GnRH for pituitary binding sites. A more rapid suppression of gonadotropin release from the pituitary gland can be achieved, in comparison with that of agonists, enabling shorter treatment regimes in ovarian hyperstimulation for assisted reproduction.[57] GnRH antagonists are not like agonists, which cause flare-up stimulation of gonadotropin and ovarian steroid hormone release. Therefore, they have the theoretical advantage of working faster and more effectively than GnRH agonists with an earlier improvement of symptoms. A representative study demonstrated that subcutaneous injection of the GnRH antagonists significantly reduces the size of endometriotic lesions in a dose-dependent manner in a rat model.[58] A pilot study reported a total of fifteen women who received a treatment protocol with 3 mg of cetrorelix (Cetrotide) weekly for eight weeks. All patients

reported a symptom-free period during GnRH antagonist treatment. Regression occurred in more than half of the cases and the degree of endometriosis declined to a mild stage on second look laparoscopy. Preserving basic estrogen production during the course of GnRH antagonist treatment apparently does not influence regression of disease, and has no major side effects.[59]

GnRH antagonists seem to be useful in the treatment of endometriosis in most cases. Furthermore, fewer side effects, such as postmenopausal symptoms, occur with this agent and no estradiol add-back is needed. In the future, new nonpeptic GnRH antagonists are expected to be available for oral administration. Although they are still under investigation, these agents have the potential to improve patients' comfort and compliance.[60]

Mifepristone (progesterone antagonist)

Mifepristone (RU 486) is an oral active progesterone antagonist at the receptor level. It also has a high affinity for progesterone and glucocorticoid II receptors. With its antiprogesterone effect, mifepristone prevents progesterone from exerting its action. It also has a direct inhibitory effect on human endometrial cells[61] and it can modulate the estrogen and progesterone receptor expression in both eutopic and ectopic endometrium.[62] In addition, mifepristone is effective in decreasing the size of endometriotic implants in a primate model.[63] Kettel et al published a series of studies of administration of different doses of mifepristone in women with endometriosis.[64-66] A minimum dose of 50 mg mifepristone for six months demonstrated a significant regression in visible endometriotic lesions and a decrease in clinical symptoms. On the other hand, treatment of endometriosis patients with mifepristone 5 mg per day in an uncontrolled pilot study resulted in pain improvement but no change in endometriosis lesions, suggesting this dosage is too low to achieve acceptable efficacy.[67] There is concern about the safety of long- term treatment because of the antiglucocorticoid properties of mifepristone. Hypoadrenalism must be considered as a major side effect of long-term treatment, especially with e doses over 200 mg per day.[16] Further large randomized clinical trials on the use of mifepristone in women with endometriosis should be performed in the future.

Selective progesterone receptor modulators (SPRM)

SPRM are novel progesterone receptor ligands with a high degree of endometrial selectivity that exhibit agonist/antagonist effects in vivo based on the target tissue.[68] They have the potential to induce reversible amenorrhea through selective inhibition of endometrial proliferation, a direct effect on endometrial blood vessels and the potential to suppress endometrial prostaglandin production in a tissue-specific manner without the systemic effects of estrogen deprivation, providing a rationale for the treatment of endometriosis -related pain.[69] Asoprisnil is the first SPRM to reach an advanced stage of clinical development for the treatment of endometriosis. Asoprisnil can suppress both the menstrual cycle and endometrial growth.[70] To date, only one randomized, placebo-controlled, dose-finding phase II study of asoprisnil has been conducted in subjects with pain from endometriosis.[71] One hundred thirty patients with a laparoscopic diagnosis of endometriosis were treated with asoprisnil (5, 10, and 25 mg) for twelve weeks. All three asoprisnil doses significantly reduced the dysmenorrhea from endometriosis in comparison with a placebo. A separate study with an identical design using different asoprisnil doses showed that 5 mg is the minimum effective dose for pain relief in subjects with endometriosis.[72] Both studies also confirmed favorable safety and tolerability profiles of asoprisnil during short-term treatment. No serious, drug-related adverse events were reported during the treatment or follow-up period.

Levonorgestrel-releasing intrauterine system

Levonorgestrel is a potent steroid widely used in oral contraceptives and subdermally implanted contraceptive devices. It is a T-shaped intrauterine system which after insertion releases the hormone levonorgestrel into the womb. The use of the intrauterine releasing system with levonorgestrel has revealed some additional health benefits other than contraception, including treatment of menorrhagia and inhibition of endometrium proliferation during postmenopausal estrogen therapy. The release rate of levonorgestrel from the intrauterine releasing system is 20 μg per 24 hours during the first year, and it slowly decreases throughout the 5 years of use, inducing the endometrium to become atrophic and inactive.[73] Because of this profound effect on the endometrium,

this device is an alternative in the medical treatment of women suffering from endometriosis, adenomyosis, chronic pelvic pain, and dysmenorrhea, as well as menorrhagia. For women with endometriosis who need long-term treatment, the levonorgestrel-releasing intrauterine system may be a treatment of choice since it permits the same system to be used for at least 5 years with no modifications in estrogen levels and few hypoestrogenic side effects.[74-76]

Future development of new drugs for endometriosis

Medical treatment options for endometriosis currently under investigation include immunomodulating drugs (pentoxifylline and loxoribine) that inhibit the effect of tumor necrosis factor (TNF)-α, matrix metalloproteinase (MMP), and angiogenesis.[23] Therapeutic manipulation of the immune system through TNF-α inhibitors may be beneficial in women with endometriosis.[77] The MMPs are a family of endopeptidases that are capable of degrading components of the extracellular matrix. It is important to many physiological and pathological processes, including embryo implantation, cyclic endometrial breakdown and endometriosis, and is regulated by its natural occurring inhibitor, tissue inhibitors of matrix metalloproteinase (TIMPs).[78,79] Suppressing the action of secreted MMPs from human ectopic endometrium with TIMP-1significantly inhibited the establishment of endometriosis lesions in a nude mice model.[80] Several cytokines may also play a role in the treatment of endometriosis. A major function of interleukin-12 (IL-12) and IL-18 is the regulation of the adaptive immune response.[81] IL-12 induces other cytokines, particularly interferon-γ (IFN-γ), which coordinate the ensuing immune response. Intraperitoneal injection of IL-12 in a murine model of endometriosis demonstrated a significant reduction of ectopic endometrial implantation.[82]

Conclusion

A better understanding of the molecular mechanism of endometriosis will result in innovative new treatments in the future. Many of these promising new agents are currently in clinical trials to evaluate efficacy and side effects, and subsequently may better reproductive outcomes. Therefore prospective, randomized clinical trials will then be needed to compare the effectiveness of these drugs with current modalities in the medical treatment of patients with endometriosis.

REFERENCES

1. Houston DE, Noller KL, Melton LJ, Selwyn BJ. The epidemiology of pelvic endometriosis. Clin Obstet Gynecol 1988;31:787-800.
2. Cramer DW, Missmer SA. The epidemiology of endometriosis. Ann N Y Acad Sci 2002;955:11-22.
3. Sensky TE, Liu DT. Endometriosis: associations with menorrhagia, infertility and oral contraceptives. Int J Gynaecol Obstet 1980;17:573-6.
4. Eskenazi B, Warner ML. Epidemiology of endometriosis. Obstet Gynecol Clin North Am 1997;24:235-58.
5. Crosignani P, Olive D, Bergqvist A, Luciano A. Advances in the management of endometriosis: an update for clinicians. Hum Reprod Update 2006;12:179-89.
6. American Fertility Society. Classification of endometriosis. Fertil Steril 1979;32:633-45.
7. American Fertility Society. Revised American Fertility Society Classification of endometriosis. Fertil Steril 1985;43:351-2.
8. Kuohung W, Jones GL, Vitonis AF, Cramer DW, Kennedy SH, Thomas D, Hornstein MD. Characteristics of patients with endometriosis in the United States and the United Kingdom. Fertil Steril 2002;78:767-72.
9. Candiani GB, Fedele L, Vercellini P, Bianchi S, DiNola G. Repetitive conservative surgery for recurrence of endometriosis. Obstet Gynecol 1991;77:421-4.
10. Practice Committee of the American Society for Reproductive Medicine. Endometriosis and infertility. Fertil Steril 2004;81:1441-6.
11. Olive DL, Lindheim SR, Pritts EA. New medical treatments for endometriosis. Best Pract Res Clin Obstet Gynaecol 2004;18:319-28.
12. Lessey BA. Medical management of endometriosis and infertility. Fertil Steril 2000;73:1089-96.
13. Valle RF, Sciarra JJ. Endometriosis: treatment strategies. Ann N Y Acad Sci 2003;997:229-39.
14. Wheeler JM, Knittle JD, Miller JD. Depot leuprolide versus danazol in treatment of women with symptomatic endometriosis. I. Efficacy results. Am J Obstet Gynecol 1992;167:1367-71.
15. Rock JA, Truglia JA, Caplan RJ. Zoladex (goserelin acetate implant) in the treatment of endometriosis: a randomized comparison with danazol. The Zoladex Endometriosis Study Group. Obstet Gynecol 1993;82:198-205.
16. Ferrero S, Abbamonte LH, Anserini P, Remorgida V, Ragni N. Future perspectives in medical treatment of endometriosis. Obstet Gynecol Surv 2005;60:817-26.
17. Vercellini P, Trespidi L, Colombo A. A gonadotropin-releasing hormone agonist versus a low-dose oral contra-

ceptive for pelvic pain associated with endometriosis. Fertil Steril 1993;60:75-9.
18. Waller KG, Shaw RW. Gonadotropin-releasing hormone analogues for the treatment of endometriosis: long-term follow-up. Fertil Steril 1993;59:511-5.
19. Vercellini P, Trespidi L, DeGiorgi O, Cortesi I, Parazzini F, Crosignani PG. Endometriosis and pelvic pain. Relation to disease stage and localization. Fertil Steril 1996;65:299-304.
20. Rice VM. Conventional medical therapies for endometriosis. Ann N Y Acad Sci 2002;955:343-52.
21. Vercellini P, De Giorgi O, Mosconi P, Stellato G, Vicentini S, Crosignani PG. Cyproterone acetate versus a continuous monophasic oral contraceptive in the treatment of recurrent pelvic pain after conservative surgery for symptomatic endometriosis. Fertil Steril 2002;77:52-61.
22. Hompes PG, Mijatovic V. Endometriosis: the way forward. Gynecol Endocrinol 2007;23:5-12.
23. Olive DL. Medical therapy of endometriosis. Semin Reprod Med 2003;21:209-22.
24. Oral E, Arici A. Peritoneal growth factors and endometriosis. Semin Reprod Endocrinol 1996;14:257-67.
25. Dmowski WP, Cohen MR. Treatment of endometriosis with an antigonadotropin, danazol: A laparoscopic and histologic evaluation. Obstet Gynecol 1975;46:147-54.
26. Buttram VC, Reiter RC, Ward S. Treatment of endometriosis with danazol: report of a 6-year prospective study. Fertil Steril 1985;43:353-60.
27. Kauppila A. Changing concepts of medical treatment of endometriosis. Acta Obstet Gynecol Scand 1993;72:324-36.
28. Mizutani T, Nishiyama S, Amakawa I, Watanabe A, Nakamuro K, Terada N. Danazol concentrations in ovary, uterus, and serum and their effect on the hypothalamic-pituitary-ovarian axis during vaginal administration of a danazol suppository. Fertil Steril 1995;63:1184-9.
29. Igarashi M, Iizuka M, Abe Y, Ibuki Y. Novel vaginal danazol ring therapy for pelvic endometriosis, in particular deeply infiltrating endometriosis. Hum Reprod 1998;13:1952-6.
30. Cobellis L, Razzi S, Fava A, Severi FM, Igarashi M, Petraglia F. A danazol-loaded intrauterine device decreases dysmenorrhea, pelvic pain, and dyspareunia associated with endometriosis. Fertil Steril 2004;82:239-40.
31. Henzl MR, Corson SL, Moghissi K, Buttram VC, Berqvist C, Jacobson J. Administration of nasal nafarelin as compared with oral danazol for endometriosis. A multicenter double-blind comparative clinical trial. N Engl J Med 1988;318:485-9.
32. Kennedy SH, Williams IA, Brodribb J, Barlow DH, Shaw RW. A comparison of nafarelin acetate and danazol in the treatment of endometriosis. Fertil Steril 1990;53:998-1003.
33. The Nafarelin European Endometriosis Trial Group (NEET). Nafarelin for endometriosis: a large-scale, danazol-controlled trial of efficacy and safety, with 1-year follow-up. Fertil Steril 1992;57:514-22.
34. Barbieri RL, Evans S, Kistner RW. Danazol in the treatment of endometriosis: analysis of 100 cases with a 4-year follow-up. Fertil Steril 1982;37:737-46.
35. Pellicer A, Simon C, Miro F, Castellvi RM, Ruiz A, Ruiz M, Perez M, Bonilla-Musoles F. Ovarian response and outcome of in-vitro fertilization in patients treated with gonadotropin-releasing hormone analogues in different phases of the menstrual cycle. Hum Reprod 1989;4:285-9.
36. Pellicer A, Tarin JJ, Miro' F, Sampaio M, De los Santos MJ, Remohi J. The use of gonadotropin releasing-hormone analogues (GnRHa), in in-vitro fertilization: some clinical and experimental investigations of a direct effect on the human ovary. Hum Reprod 1992;7:39-47.
37. Emons G, Schally AV. The use of luteinizing hormone releasing hormone agonists and antagonists in gynaecological cancers. Hum Reprod 1994;9:1364-79.
38. Chegini N, Rong H, Dou Q, Kipersztok, Williams RS. Gonadotropin-releasing hormone (GnRH) and GnRH receptor gene expression in human myometrium and leiomiomata and the direct action of GnRH analogs on myometrial smooth muscle cells and interaction with ovarian steroids in vitro. J Clin Endocrinol Metab 1996;81:3215-22.
39. Hsueh AJW, Jones PBC. Extrapituitary actions of gonadotropin releasing hormone. Endocr Rev 1981;2:437-55.
40. Sagsveen M, Farmer JE, Prentice A, Breeze A. Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density. Cochrane Database Syst Rev 2003;4:CD001297.
41. Waller KG, Shaw RW. Gonadotropin-releasing hormone analogues for the treatment of endometriosis: long-term follow-up. Fertil Steril 1993;59:511-5.
42. Greep RO, Van Dyke HB, Chow BF. Gonadotropin of swine pituitary: various biological effects of purified thylkentrin (FSH) and pure matakentrin (ICSH). Endocrinology 1942;30:635-49.
43. Simpson ER, Mahendroo MS, Means GD, Kilgore MW, Hinshelwood MM, Graham-Lorence S, Amarneh B, Ito Y, Fisher CR, Michael MD. Aromatase cytochrome P450, the enzyme responsible for estrogen biosynthesis. Endocr Rev 1994;15:342-55.
44. Simpson ER, Clyne C, Rubin G, Boon WC, Robertson K, Britt K, Speed C, Jones M. Aromatase-a brief overview. Annu Rev Physiol 2002;64:93-127.
45. Bulun SE, Zeitoun K, Takayama K, Noble L, Michael D, Simpson E, Johns A, Putman M, Sasano H. Estrogen production in endometriosis and use of aromatase inhibitors to treat endometriosis. Endocr Relat Cancer 1999;6:293-301.
46. Zeitoun KM, Bulun SE. Aromatase: a key molecule in the pathophysiology of endometriosis and a therapeutic target. Fertil Steril 1999;72:961-9.

47. Buzdar A, Howell A. Advances in aromatase inhibition: clinical efficacy and tolerability in the treatment of breast cancer. Clin Cancer Res 2001;7:2620-35.
48. Goss PE, Strasser K. Aromatase inhibitors in the treatment and prevention of breast cancer. J Clin Oncol 2001;19:881-94.
49. Buzdar AU, Robertson JF, Eiermann W, Nabholtz JM. An overview of the pharmacology and pharmacokinetics of the newer generation aromatase inhibitors anastrozole, letrozole, and exemestane. Cancer 2002;95:2006-16.
50. Santen RJ, Harvey HA. Use of aromatase inhibitors in breast carcinoma. Endocr Relat Cancer 1999;6:75-92.
51. Oktay K, Hourvitz A, Sahin G, Oktem O, Safro B, Cil A, Bang H. Letrozole reduces estrogen and gonadotropin exposure in women with breast cancer undergoing ovarian stimulation before chemotherapy. J Clin Endocrinol Metab 2006;91:3885-90.
52. Ailawadi RK, Jobanputra S, Kataria M, Gurates B, Bulun SE. Treatment of endometriosis and chronic pelvic pain with letrozole and norethindrone acetate: a pilot study. Fertil Steril 2004;81:290-6.
53. Shippen ER, West WJ Jr. Successful treatment of severe endometriosis in two premenopausal women with an aromatase inhibitor. Fertil Steril 2004;81:1395-8.
54. Soysal S, Soysal ME, Ozer S, Gul N, Gezgin T. The effects of post-surgical administration of goserelin plus anastrozole compared to goserelin alone in patients with severe endometriosis: a prospective randomized trial. Hum Reprod 2004;19:160-7.
55. Attar E, Bulun SE. Aromatase inhibitors: the next generation of therapeutics for endometriosis? Fertil Steril 2006;85:1307-18.
56. Huirne JA, Lambalk CB. Gonadotropin-releasing-hormone-receptor antagonists. Lancet 2001;358:1793-803.
57. Griesinger G, Felberbaum R, Diedrich K. GnRH-antagonists in reproductive medicine. Arch Gynecol Obstet 2005;273:71-8.
58. Jones RC. The effect of a luteinizing hormone-releasing hormone antagonist on experimental endometriosis in the rat. Acta Endocrinol 1987;114:379-82.
59. Kupker W, Felberbaum RE, Krapp M, Schill T, Malik E, Diedrich K. Use of GnRH antagonists in the treatment of endometriosis. Reprod Biomed Online 2002;5:12-6.
60. Finas D, Hornung D, Diedrich K, Schultze-Mosgau A. Cetrorelix in the treatment of female infertility and endometriosis. Expert Opin Pharmacother 2006;7:2155-68.
61. Murphy AA, Zhou MH, Malkapuram S, Santanam N, Parthasarathy S, Sidell N. RU486-induced growth inhibition of human endometrial cells. Fertil Steril 2000;74:1014-9.
62. Jiang J, Wu RF, Wang ZH, Sun HC, Xu Z, Xiu HM. Effect of mifepristone on estrogen and progesterone receptors in human endometrial and endometriotic cells in vitro. Fertil Steril 2002;77:995-1000.
63. Grow DR, Williams RF, Hsiu JG, Hodgen GD. Antiprogestin and/or gonadotropin-releasing hormone agonist for endometriosis treatment and bone maintenance: a 1-year primate study. J Clin Endocrinol Metab 1996;81:1933-9.
64. Kettel LM, Murphy AA, Mortola JF, Liu JH, Ulmann A, Yen SS. Endocrine responses to long-term administration of the antiprogesterone RU486 in patients with pelvic endometriosis. Fertil Steril 1991;56:402-7.
65. Kettel LM, Murphy AA, Morales AJ, Yen SS. Clinical efficacy of the antiprogesterone RU486 in the treatment of endometriosis and uterine fibroids. Hum Reprod 1994;9(suppl 1):116-20.
66. Kettel LM, Murphy AA, Morales AJ, Ulmann A, Baulieu EE, Yen SS. Treatment of endometriosis with the antiprogesterone mifepristone (RU486). Fertil Steril 1996;65:23-8.
67. Kettel LM, Murphy AA, Morales AJ, Yen SS. Preliminary report on the treatment of endometriosis with low-dose mifepristone (RU 486). Am J Obstet Gynecol 1998;178:1151-6.
68. Elger W, Bartley J, Schneider B, Kaufmann G, Schubert G, Chwalisz K. Endocrine pharmacological characterization of progesterone antagonists and progesterone receptor modulators with respect to PR-agonistic and antagonistic activity. Steroids 2000;65:713-23.
69. Chwalisz K, Garg R, Brenner RM, Schubert G, Elger W. Selective progesterone receptor modulators (SPRMs): a novel therapeutic concept in endometriosis. Ann N Y Acad Sci 2002;955:373-88.
70. DeManno D, Elger W, Garg R, Lee R, Schneider B, Hess-Stumpp H, Schubert G, Chwalisz K. Asoprisnil (J867): a selective progesterone receptor modulator for gynecological therapy. Steroids 2003;68:1019-32.
71. Chwalisz K, Mattia-Goldberg K, Lee M, Elger W, Edmonds A. Treatment of endometriosis with the novel selective progesterone receptor modulator (SPRM) asoprisnil. Fertil Steril 2004;82:S83-4.
72. Chwalisz K, Perez MC, Demanno D, Winkel C, Schubert G, Elger W. Selective progesterone receptor modulator development and use in the treatment of leiomyomata and endometriosis. Endocr Rev 2005;26:423-38.
73. Luukkainen T, Lahteenmaki P, Toivonen J. Levonorgestrel-releasing intrauterine device. Ann Med 1990;22:85-90.
74. Lockhat, FB, Emembolu JO, Konje JC. The efficacy, side-effects and continuation rates in women with symptomatic endometriosis undergoing treatment with an intra-uterine administered progestogen (levonorgestrel): a 3 year follow-up. Hum Reprod 2005;20:789-93.
75. Bahamondes L, Petta CA, Fernandes A, Monteiro I. Use of the levonorgestrel-releasing intrauterine system in women with endometriosis, chronic pelvic pain and dysmenorrhea. Contraception 2007;75:S134-9.
76. Petta CA, Ferriani RA, Abrao MS, Hassan D, Rosa E Silva JC, Podgaec S, Bahamondes L. Randomized clinical trial of a levonorgestrel-releasing intrauterine system and

a depot GnRH analogue for the treatment of chronic pelvic pain in women with endometriosis. Hum Reprod 2005;20:1993-8.
77. D'Antonio M, Martelli F, Peano S, Papoian R, Borrelli F. Ability of recombinant human TNF binding protein-1 (r-hTBP-1) to inhibit the development of experimentally-induced endometriosis in rats. J Reprod Immunol 2000;48:81-98.
78. Huang HY, Wen Y, Irwin JC, Kruessel JS, Soong YK, Polan ML. Cytokine mediated regulation of 92-kilodalton type IV collagenase, tissue inhibitor of metalloproteinase-1 (TIMP-1), and TIMP-3 messenger ribonucleic acid expression in human endometrial stromal cells. J Clin Endocrinol Metab 1998;83:1721-9.
79. Huang HY. The cytokine network during embryo implantation. Chang Gung Med J 2006;29:25-36.
80. Bruner KL, Matrisian LM, Rodgers WH, Gorstein F, Osteen KG. Suppression of matrix metalloproteinases inhibits establishment of ectopic lesions by human endometrium in nude mice. J Clin Invest 1997;99:2851-7.
81. Huang HY, Chan SH, Yu HT, Wang HS, Lai CH, Soong YK. Interleukin-18 system messenger ribonucleic acid and protein expression in human endometrium during menstrual cycle. Fertil Steril 2006;86:905-13.
82. Somigliana E, Vigano P, Rossi G, Carinelli S, Vignali M, Panina-Bordignon P. Endometrial ability to implant in ectopic sites can be prevented by interleukin-12 in a murine model of endometriosis. Hum Reprod 1999;14:2944-50.

子宮內膜異位症之內科療法

黃泓淵

子宮內膜異位症是婦科常見之良性疾病，是子宮內膜組織出現在子宮腔外的一種病變。子宮內膜異位症的發生與雌激素有密切關係，因此好發於生殖年齡女性。臨床上常合併經痛、不孕，診斷與治療除需藉助手術療法外，內科療法亦有相當之成效。子宮內膜異位之內科療法是以阻斷雌激素之作用進而抑制子宮內膜異位症病灶之增生，常用之傳統內科療法包括了口服避孕藥、雄性荷爾蒙製劑、黃體素及促性腺激素釋放荷爾蒙類似體。由於子宮內膜異位症具有高復發率之特性，因此若需長時間或重複周期性治療，則需考慮其藥物副作用。拜醫學發展之賜，對於子宮內膜異位症其分子與細胞學之生物機轉日益了解，新的子宮內膜異位症內科療法蓬勃發展。包含了促性腺激素釋放荷爾蒙擷抗劑、芳香酶抑制劑、選擇性黃體素受體調節劑、黃體素擷抗劑與子宮內黃體素釋放系統。這些新的內科療法對於子宮內膜異位症之控制均有預期之療效，未來仍需大型前瞻性之臨床試驗，來證實新的內科療法在子宮內膜異位症之治療成效與藥物副作用是否比傳統內科療法爲佳。(長庚醫誌 2008;31:431-40)

關鍵詞：子宮內膜異位症，促性腺激素釋放荷爾蒙，黃體素，芳香酶抑制劑

長庚紀念醫院 台北院區 婦產部；長庚大學 醫學院
受文日期：民國96年6月29日；接受刊載：民國97年1月3日
通訊作者：黃泓淵醫師，長庚紀念醫院 婦產部。桃園縣333龜山鄉復興街5號。Tel.: (03)3281200轉8251; Fax: (03)3288252; E-mail: hongyuan@cgmh.org.tw