Modern Treatment for Endometriosis

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Abstract

Endometriosis is defined as the presence of endometrial tissue outside the uterus, which induces a chronic, inflammatory reaction in the affected tissues (most commonly the ovaries, the peritoneal cavity and fallopian tubes). The precise mechanisms by which endometrial tissue reaches these ectopic locations are still unknown. The pathogenic hypotheses developed so far are controversial, although the most cited theory is that of retrograde menstruation. Other additional pathogenic factors are immunologic abnormalities, peritoneal dysfunction and endometrial disorders.

The aim of this paper is to provide updated information about the modern possibilities of the treatment in endometriosis, based on the basic pathogenic mechanisms of the disease. In our opinion, treatment must be individualized and the therapeutic options should be examined in the light of the presenting symptoms and associated infertility. Another aspect to be considered is the impact of the disease as well as the effect of its treatment on the quality of life.
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The therapeutic strategies for endometriosis have evolved in times simultaneously with the evolution of knowledge of pathogenic mechanisms involved in the occurrence and progression of the endometrial implants. For these pathogenic mechanisms, a series of active pharmacological substances as well as various surgical techniques have developed in time. Recent intensive research, focused on identifying and understanding the pathogenic mechanisms of endometriosis, led to the development of new therapeutic lines, both in respect of new therapeutic drugs and new ways of administration.

The therapeutically options currently used are:

- **Observation**, which is a "wait-and-see" approach.
- **Hormonal treatment**, which ensures the temporary regression of the endometriotic lesions, relieving symptoms.
- **Surgical treatment**, which can be a conservative treatment consisting in the removal of visible lesions, or, as a last resort, a radical treatment consisting in the removal of the affected reproductive organs.

1. Observation approach

The observation can be recommended as the initial conservative approach for infertile patients with a superficial illness and reduced or absent symptomatology, or for perimenopausal patients.

The observation approach is a non-interventional therapeutic strategy or a minimal intervention (antiprostaglandinic medication for relieving the pain) which is mainly based on monitoring the evolution of the disease(1).

For patients with incipient or moderate endometriosis who wish to remain pregnant a period of 6 months up to 1 year of unprotected sexual contact may be recommended. If pregnancy does not meanwhile occur another therapeutic strategy can be used.

Several studies reported similar pregnancy rates following the observation approach versus medical or hormonal treatment or conservative surgical treatment (consisting in the removal of the endometrial implants)[(2)].

Premenopausal patients (even if having a severe form of the disease) often need no treatment because following menopause the estrogenic stimulus

ceases and the endometrial implants decrease in size leading to the regression of the disease.

2. Medical treatment

The multiple medical strategies in endometriosis are targeted to the hormonal alteration of the menstrual cycle attempting to induce a state of pseudo-pregnancy, pseudo-menopause or chronic anovulation. All these situations generate an environment which is hostile to the growing, developing and expansion of the endometrial implants[3].

2.1. Analgesic treatment

2.1.1. Nonsteroidal anti-inflammatory drugs

The analgesic treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) is the first-in-line treatment in an endometriosis characterized by minimal or medium pain.

NSAIDs block the synthesis of prostaglandins (hormone-like substances involved in endometrial pain and inflammation). They are effective in relieving dysmenorrhea in about 80% of patients. However pain relief can be incomplete since the mechanisms which trigger the pain in endometriosis are complex, involving multiple other factors besides prostaglandins. It is important to note that NSAIDs have significant adverse effects, like gastric ulcerations and anovulatory effects when taken at mid-cycle.

2.1.2. Other analgesic drugs

Tramadol is prescribed as second line medication. The usual dose is 100-200 mg per day, but it has to be prescribed with caution for the patients with epilepsy and for those who use at the same time monoamine oxidase inhibitors (IMAO).

2.2. Hormonal treatment

2.2.1. Danazol

Danazol (Danocrine) is an androgenic synthetic substance which influences the hypothalamic and pituitary glands, inhibiting the secretion of FSH and LH and the consecutive reduction of the ovarian steroidogenesis. The subsequent atrophy of the endometrial implants leads to the relieving of the symptoms. It appears that Danazol might also influence the immune system by decreasing the concentration of autoantibodies with beneficial effects in endometriosis[4]. Part of the Danazol's efficiency is also due to the effect of GnRH suppression and of gonadotropin secretion as well as to the increase the metabolic clearance of estradiol and progesterone.

Based on all these effects Danazol induces an environment in which the increased levels of androgens and the very low levels of estrogens obstruct the progression of endometriosis; the amenorrhea induced prevents the formation of new endometrial implants in the peritoneal cavity[5].

The therapy must be started when the patient is menstruating. The initial dose is usually 800 mg per day (divided in two oral doses). Patients with less severe symptoms may be given 200 to 400 mg per day, divided in two oral doses. The duration of the treatment is 6-9 months.

The Danazol adverse effects include estrogen deficiency (flushing, sweating, atrophic vaginitis) and androgenic effects (hirsutism, weight gain and acne).

2.2.2. GnRH agonists

GnRH agonists are substances chemically similar to the natural hormone GnRH. These synthetic analogues increase the blood levels for LH and FSH, leading initially to an increase of gonadic steroids. For this reason, in certain situations, an aggravation of the symptomatology can occur during the first month of treatment[6]. However, continuous administration induces a strong down-regulation of the pituitary receptors for GnRH, with a strong decrease in FSH and LH levels; the cessation of the cyclic secretion of the ovarian hormones induces a pseudo-menopausal state characterized by hypoestrogenism and amenorrhea. As far as pain relieve is concerned the efficacy of the agonists is similar to that of Danazol[7].

GnRH agonists reduce the level of ovarian hormones down to levels identified in patients in menopause (or whose ovaries had been surgically removed) in 2 to 4 weeks. Ovulation and menstruation are resumed as soon as the treatment is withdrawn[8].

The agonist medication leads to an almost complete alleviation of the symptomatology usually in 4 weeks. In many cases the laparoscopic examination confirmed the complete regression of lesions[9]. Just like Danazol, GnRH agonists are more efficient in superficial lesions and less efficient in endometriomas; they have no effect in adhesions and scar tissues.

The leuprolide dose is 3.75 mg (single intramuscular injection, monthly). Possible leuprolide side effects are decreased bone density and estrogen deficiency.

Goserelin can be administered in a 3.6 mg dose (subcutaneously, every 28 days). The estrogen deficiency is one of the major inconveniences of the treatment with Zoladex.

Nafarelin is available as a nasal spray to be used twice daily (400 mg). Adverse effects include estrogen deficiency, bone density changes and nasal irritation.

2.3. Synthetic progestatives

Synthetic progestatives limit the estrogen-dependent growth of the endometriotic tissue and long term therapy with these substances induces endometrial atrophy. The progestatives also inhibit the secretion of the pituitary gonadotropins and the ovarian production of steroids and also have a mild androgenic effect[6].

The analgesic effect has been reported as excellent, more than 80% of treated patients presenting complete or partial alleviations of pelvic pain.

As regards infertility, it appears that it is not influenced by progestatives. In a nonrandomized study on patients with incipient illness treated with medroxyprogesterone acetate, Danazol or observation approach therapy, the pregnancy rates during a period of 18 months had been similar. For this reason infertility as the sole symptom of the disease does not justify the utilization of synthetic progestatives.

Synthetic progestational agents can be administered orally or by injection. Medroxyprogesterone can be administered orally, 5-20 mg per day. Possible adverse effects include weight gain, depression, irregular menses or amenorrhea. Medroxyprogesterone suspension is administered as intramuscular injection (100 mg per dose) every two weeks for two months and then once a month for four months (200 mg per dose). The side effects are the same with oral progestins

2.4. Oral contraceptives

Low doses of combined oral contraceptives (COC) (estrogen and progesteron) are often prescribed for the treatment of dysmenorrhea and of other

symptoms in endometriosis. They can be administered in cycles (3 weeks) or continuously without any interruption[10]. This latter option induces the so called "pseudo-pregnancy" state and has been used for several decades, often being deemed as the first line therapy in endometriosis[10].

COC inhibit FSH and LH secretion by suppressing the production of estrogens in the ovaries. This induces an initial decidualization of the endometrial tissue followed by atrophy within several months, inhibiting the growth, bleeding and inflammation of the endometrial lesions[11].

Oral contraceptives (1 pill per day) may be administered by a continuous or cyclic pattern and their side effects may include headache, nausea and hypertension.

2.5. Local hormonal treatment: new therapeutic perspectives

Intense recent research has focused on identifying and understanding the pathogenic mechanisms of endometriosis, leading to the emergence of new therapeutic strategies implying new medications as well as new methods of administration.

During the past few years a new method of administration for hormonal treatment has become more and more frequently used: the local administration (intrauterine and vaginal) of estrogens, progesterone or estro-progesterone derivatives, as substitution hormone therapies administered for contraception, for treating menorrhagia or vaginal dystrophy.

Devices of local hormone administration for progesterone derivatives (levonorgestrel) or Danazol are more and more frequently used in patients affected by endometriosis[12].

The advantages of local hormone delivery are:

- Increased efficiency due to direct local effects on target organs.
- Reduction of systemic effects.
- Patient's increased compliance with the treatment[13].

2.5.1. Intrauterine levonorgestrel (LNG-IUS)

LNG-IUS has an antiproliferative effect and can also block the estrogen receptors thus having an anti-estrogenic effect as well[13,14]. The intrauterine administration of LNG with direct distribution in pelvic tissues causes a local concentration of the progestational agent exceeding its plasmatic level[15]. The local absorption seems to be more efficient, limiting the adverse effects, thus ensuring a better patient compliance especially for long term treatment. This local hormone therapy successfully treats dysmenorrhea and chronic pelvic pain associated with deep endometriosis[16]. Its use following conservative surgical treatment for symptomatic endometriosis reduces considerably the medium risk of recurrence of moderate or severe dysmenorrhea[17].

The use of LNG-IUS is a valuable asset in the treatment of adenomyosis, its efficiency in the treatment of adenomyosis being due to the effect referred to as decidualisation, followed by subsequent marked atrophy of the endometrial and adenomyosis sites. It has been noted that LNG-IUS also induces a down-regulation of estrogenic receptors in glands as well as in the stroma of the endometrial tissue preventing estrogenic stimulation, inducing atrophy and decreasing the extent of adenomyosis[12].

2.5.2. Intrauterine Danazol

It is known that Danazol has direct effects on endometrial tissue by inhibiting DNA synthesis and inducing apoptosis. As long as the adenomatous tissue is directly connected to the surface of endometrial tissue and to uterine cavity by endometrial gland ducts, the intrauterine administration of Danazol is followed by its direct transfer to adenomatous and adjacent tissues.

Danazol has anti-angiogenic, anti-inflammatory and imunomodulatory effects, reducing vaginal bleeding (with no endometrial atrophy) and decreasing endometrial cell proliferation and differentiation[13].

The literature has documented promising results regarding the intrauterine utilization of Danazol in patients affected by adenomyosis. Indeed in these patients the use of intrauterine devices is effective in eliminating dysmenorrhea and hypermenorrhea. Moreover it appears to be also effective in infertile patients, since conception usually occurs following its removal.

In a recent prospective study lead by Cobellis L. et al, the authors have assessed the efficacy of continuous intrauterine release of Danazol in the treatment of dysmenorrhea, chronic pelvic pain and of dyspareunia associated with moderate and/or severe endometriosis[18]. The authors concluded that dysmenorrhea, dyspareunia and the chronic pelvic pain are considerably diminished from the first month of treatment ($p<0.01$) and the effect is maintained for a period of 6 months. These results show that the continuous Danazol intrauterine release represents an effective conservative treatment for the alleviation of all the painful symptoms associated with endometriosis, as well as for the control of menorrhagia occurring in adenomyosis[18].

2.5.3. Intravaginal Danazol

The vaginal administration of Danazol (vaginal ring) has been tested in several studies with promising results for treating patients with deep endometriosis[19].

The administration of Danazol vaginal gel (100 mg/0.2 ml) for 4 months resulted in the decrease of dysmenorrhea and chronic pelvic pain in 24 patients with endometriosis[12].

Upon intravaginal administration Danazol presents the following routes of diffusion:

- Direct, passive diffusion through the vaginal mucus.
- Diffusion through the venous circulation system.
- Diffusion through the lymphatic system in the upper part of the vagina, which communicates directly with that of the uterus[12].

The Razzi S. et al study assesses the therapeutic efficacy of intravaginal Danazol in deep endometriosis. This is a sonographic study based on the use of trans-vaginal or trans-rectal probes and it documented the size reduction of the lumps on rectovaginal septum level, following the intravaginal administration of Danazol[13].

2.6. Aromatasis inhibitors

Aromatasis inhibitors have been initially investigated in postmenopausal patients with mammary neoplasm. Now they are being assessed in premenopausal patients that underwent ovary ablation or suppression. Anastrozol and Letrozol are currently successfully used in the treatment of endometriosis in postmenopausal as well as in premenopausal patients[20].

In premenopausal patients the association of some ovary suppressors to aromatasis inhibitors is required, or else the estrogenic depletion increases the FSH and LH secretion with ovary stimulation[20].

GnRH agonists, progestin, progesterone or combined oral contraceptives have been associated to aromatasis inhibitors, all of them having an obvious positive effect in alleviating the pelvic pain.

3. Surgical treatment

3.1. Conservative surgical treatment

The laparoscopic intervention represents the diagnostic and therapeutic "gold standard" for endometriosis. The laparoscopy allows the biopsy of the suspected lesions and the establishment of the histological diagnosis.

The conservative laparoscopic surgical treatment consists in removing all visible areas of endometriosis by excision, fulguration (tissue destruction with electric current) or laser vaporization. The purpose of conservative therapy is to excise to the largest visible extent of endometriosis

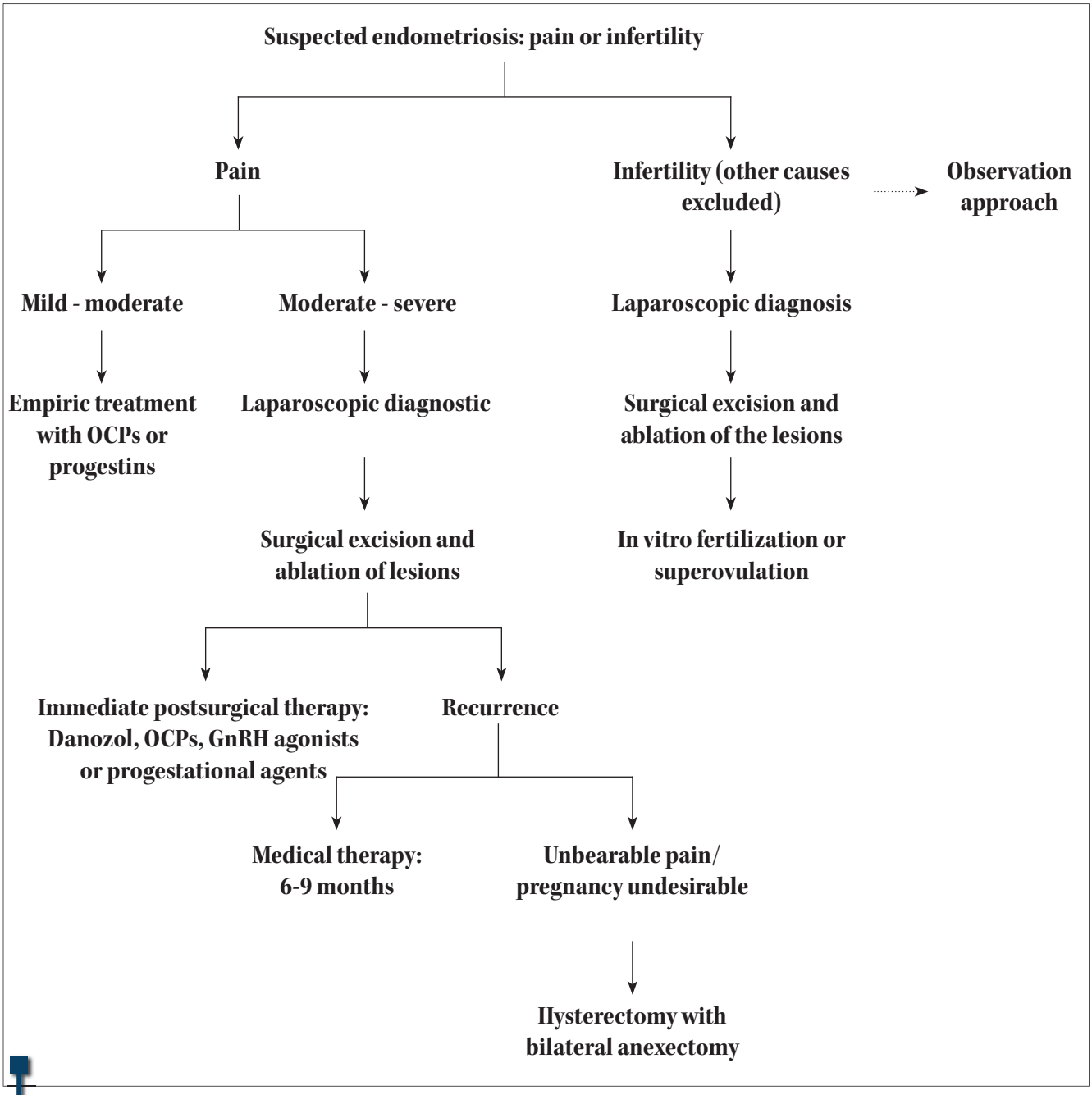

Figure 1. Symptomatology-based therapeutic algorithm in endometriosis (pain or infertility) (OCPs - oral contraceptive pills, GnRH - gonadotropin - releasing hormone)[24]

lesions (and whenever possible of adherences, too) for alleviating the pain and for reconstructing (as close to the physiological state as possible) of the pelvic anatomy, for the purpose of preserving fertility.

The treatment presents better results as far as the alleviation of the pain is concerned, with a response in at least 80% in cases of mild-moderate endometriosis[21]. Up to 90% of the patients who initially responded to the conservatory surgical treatment had not experienced relapses of pain within 1 year[21].

Unfortunately, the conservative treatment cannot guarantee the removal of microscopic endometriosis lesions and therefore relapses following this procedure are unavoidable.

The average pregnancy rate after the laparoscopic treatment ranges between 34% and 89%. The pregnancy occurring following surgical treatment seems to delay endometriosis relapses.

3.2. Radical surgical treatment

In severe endometriosis, whenever the disorder threatens the function of vital organs or severely alters the quality of life (very intense and persistent pain or different incapacities), the only therapeutic option is the radical approach, consisting of total hysterectomy with bilateral annexectomy. The treatment thus induces an abrupt and dramatic surgical menopause followed by the classical symptomatology of hypoestrogenism: flushes, vaginal atrophy, emotional liability, increased risk for osteoporosis and cardiovascular diseases[22]. In order to reduce such symptoms and to avoid long term after-effects, the low-dose estrogen (ERT - 0.625 mg/day) or conjugated estrogens hormone therapy is used. However, there is a chance that this therapy may stimulate residual endometriosis. For this reason a rigorous follow-up of the patient is required. Moreover, progesterone therapy must be associated to ERT in order to prevent the stimulation of hyperplasia and of any possible cancer lesions in the residual endometriotic tissues. In selected cases inter-annexal hysterectomy is indicated with the conservation of the ovaries.

Whenever possible, hysterectomy should be avoided in young patients willing to preserve their fertility. Young women (<30 years old) who undergo hysterectomy due to pelvic pain and endometriosis incur a higher risk for residual symptoms than women aged over 40 years[23].

3.3. Therapeutic algorithm

Figure 1 introduces a symptomatology-based therapeutic algorithm. It can be useful to gynecologists and obstetricians and has great implications in medical practice (Figure 1 - Symptomatology-based therapeutic algorithm in endometriosis - pain or infertility). ■

References

1. Weinstein L. Hormonal therapy in the patient with surgical menopause. Obstet Gynecol. 1990;75:47S-50S.
2. Badawy SZ, El Bakry MM, Samuel F, et al. Cumulative pregnancy rates in infertile women with endometriosis. J Reprod Med. 1988;33:757-60.
3. Melega C, Balducci M, Bulletti C, Galassi A, Jasonni VM, Flamigni C. Tissue factors influencing growth and maintenance of endometriosis. Ann N Y Acad Sci 1991;622:256-265.
4. Endometriosis: An Overview of the Disease and Its Treatment Journal of the American Pharmaceutical Association 40(5):645-657, 2000.
5. Selak V, Farquhar C, Prentice A, Singla A. Danazol for pelvic pain associated with endometriosis. Cochrane Database Syst Rev. 2001;(4): CD000068.
6. Prentice A, Deary AJ, Bland E. Progestagens and anti-progestagens for pain associated with endometriosis. Cochrane Database Syst Rev. 2000;(2):CD002122.
7. Heinrichs WL, Henzl MR. Human issues and medical economics of endometriosis. J Reprod Med 1998;43(3 suppl):299-308.
8. Olive D, Schwartz LB. Endometriosis. N Engl J Med 1993;328:1759-69.
9. Vercellini P, Crosignani PG, Padini R, et al. A gonadotropin-releasing hormone agonist compared with expectant management after conservative surgery for symptomatic endometriosis. Br J Obstet Gynecol. 1999;106:672-7.
10. Moore J, Kennedy S, Prentice A. Modern combined oral contraceptives for pain associated with endometriosis. Cochrane Database Syst Rev. 2000;2:CD001019.
11. Modugno F, Ness RB, Allen GO. Oral contraceptive use, reproductive history, and risk of epithelial ovarian cancer in women with and without endometriosis. Am J Obstet Gynecol. Sep 2004;191(3):733-40.
12. S. Luisi, L. Lazzeri, V. Ciani, F. Petraglia - Nuovi trattamenti medici per l'endometriosi. Ginecorama, Anno XXX - N.1 - Febbraio 2008, p. 23-27.
13. Petraglia Felice - Local hormonal treatment of endometriosis. 13th World Congress of Gynecological Endocrinology, Florence 2008.
14. Varma R, Sinha D, Gupta JK. Non-contraceptive uses of levonorgestrel-releasing hormone system (LNG-IUS)--a systematic enquiry and overview. Eur J Obstet Gynecol Reprod Biol. Mar 1 2006;125(1):9-28
15. 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.
16. Vercellini P, Frontino G, De Giorgi O, Aimi G, Zaina B, Crosignani PG. Comparison of a levonorgestrel-releasing intrauterine device versus expectant management after conservative surgery for symptomatic endometriosis: a pilot study.Fertil Steril 2003;80:305-9.
17. 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;20:19931998.
18. 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;82:239-240.
19. Janicki TI, Dmowsky WP. Intravaginal danazol significantly reduces chronic pelvic pain in women with endometriosis. Supplement to the Journal of the Society for Gynecologic Investigation (SGI) 2004 Annual Meeting, abstract no. 266.
20. Attar E, Bulun SE. Aromatase inhibitors: the next generation of therapeutics for endometriosis? Fertil Steril. 2006;85:1307-1318.
21. Jacobson TZ, Barlow DH, Garry R, Koninckx P. Laparoscopic surgery for pelvic pain associated with endometriosis. Cochrane Database Syst Rev 2001;(4):CD001300.
22. Everson SA, Matthews KA, Guzick DS, et al. Effects of surgical menopause on psychological characteristics and lipid levels. The healthy women study. Health Psychol. 1995;14:435-43.
23. MacDonald SR, Klock SC, Milad MP. Long-term outcome of non-conservative hysterectomy for endometriosis-associated pain in women < 30 yo. Am J Obstet Gynecol. 1999;180:1360-3.
24. Caroline Wellbery. Diagnosis and Treatment of Endometriosis. Am American Family Physician, vol. 60, no. 6 (october 15, 1999).