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Medical treatment of endometriosis

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The medical treatment of endometriosis is a critical aspect of the therapeutic approach to this disease. This review will present an overview of current literature about the medical treatment of endometriosis, without referring to the surgical treatment or a combination of both. The main purpose of the current medical treatment of endometriosis is to create an amenorrheic state, in other words, to create a hypoestrogenic environment by suppressing estrogen secretion of the ovary. Current research has focused upon medications designed to attack specific aspects of the development and maintenance of endometriosis. This includes progesterone receptor modulators, gonadotropin releasing hormone (GnRH) analogs, aromatase inhibitors and, tumor necrosis factor α (TNF–α) inhibitors, angiogenesis inhibitors, matrix metalloproteinase inhibitors and estrogen receptor β agonists like inmunomodulators. These drugs show decreased spreading of lesions and reduced disease related symptoms. Medical treatment is moderately effective in reducing pain but ineffective in improving fertility; a combination of medical treatment with assisted reproductive technology may be beneficial in improving fetility.

Key words: **Endometriosis, therapy - Pelvic pain - Infertility.**

Endometriosis is currently one the most enigmatic diseases within the field of gynecology; however this disease does not have an established treatment yet. According to Sampson's hypothesis in 1927, retrograde menstruation is a key factor in the pathogenesis of endometriosis, in which endometrial cells found in menstrual debris are transported up into the fallopian tubes, entering and spreading onto the peritoneal cavity.[1, 2] This occurs in reproductive age women with the presence of menstruation. If this definition is true, then the amount of retrograde menstruation could be different in women with or without endometriosis.[3, 4] Still, the gold standard for the diagnosis of endometriosis is histological confirmation of endometrial glands and estroma in extrauterine sites.[5, 6]

We have very little understanding about the relationship between endometriosis and infertility even though more than 7 000 articles have been published on the subject and, consequently, we find ourselves unaware of which procedure is most adequate to treat this disease. However, endometriosis has been treated and it is continually being treated with diverse drugs such as estrogens, an estrogen and progestin combination, danazol, gestrinone and GnRH analogs (GnRHa).[7-10] Recent studies present

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attractive new alternatives for the treatment of this disease, using drugs such as aromatase inhibitors, immunomodulators and selective progesterone receptor modulators (SPRMs). These drugs show decreased spreading of lesions and reduced disease related symptoms.[11, 12]

The central dogma guiding medical management of endometriosis is the observation that sex steroid hormones are the major regulators of growth and function of endometriotic lesions. This view is supported by both laboratory and clinical observations. Most endometriotic lesions contain estradiol progesterone and androgen receptors. In general, estradiol promotes growth in endometriotic lesions, androgens cause atrophy, and progestins can cause complex effect, depending on the dose and progestin used.

The present review tries to analyze the current literature about medical treatment of endometriosis, without referring to surgical treatment or a combination of both.

Diagnosis

The improvement in the various imaging and endoscopic techniques, as well as serologic tests, the correct diagnosis of the disease is becoming more precise and easier.

Currently, laparoscopy is considered as gold standard diagnostic test looking for evidence of all types and stages of endometriosis. With the advent of laparoscopic techniques, frequency of diagnosis of endometriosis at laparoscopy has increased dramatically by visualization of typical and atypical lesions.[13, 14]

The main clinical manifestations of endometriosis are pain and infertility. Nowadays there are different established treatments aiming to reduce the discomfort of the patient and to improve pregnancy rates. However, pain represents the mayor clinical problem of the disease, basically dysmenorrhea (60%), pelvic pain (40-50%), lower abdominal pain, and dyspareunia (40-50%).

The classification of the American Society for Reproductive Medicine is based on a twenty-point scale and includes 4 stages. Minimal (stage I) and mild (stage II) disease are both characterized by scattered, superficial implants on structures other than uterus tubes or ovaries, with no associated scarring or significant adhesions and rare or superficial implants on ovaries. Moderate (stage III) disease is characterized by multiple implants or small endometriomas (≤2 cm) involving one or both ovaries; minimal peritubular or periovarian adhesions; and scattered, scarred implants on other structures. Severe (stage IV) disease is characterized by large ovarian endometriomas, significant tubal or ovarian adhesions, tubal obstruction, obliteration of the cul-de-sac, major uterosacral involvement, and significant bowel or urinary tract disease.[15]

The classic endometriotic implant is the dark, blue-black, powder-burn lesion that typically lies under the peritoneal surface. Only recently have we come to appreciate that endometriosis may appear in many other forms. So called atypical lesions may vary in color from red to brown, black, white or yellow. Their appearance depends in part on their localization or blood supply. A variety of pathologic lesions are confused visually with endometriosis implants. Hemangiomas, inflammatory changes, mesothelial hyperplasia, hemosiderin deposition or endosalpingiosis may be mistaken for endometriosis.

Although laparoscopy is regarded as the gold standard diagnostic test for endometriosis, diagnostic laparoscopy is associated with 0.06% risk of major complications and this risk is increased to 1.3% in operative laparoscopy.[6]

No laboratory findings are particularly helpful in making or confirming a diagnosis of endometriosis. An association between endometriosis and CA-125 has been reported, but, may be of value only in women with severe endometriosis. Other makers have been proposed in the diagnostic of minimal – mild endometriosis (Ca 19-9, SICAM-1, PP14, IL6, TNF, autoantibodies, EGR-1, P450 aromatase), although significant overlapping exists between patients with endometriosis and disease free women.[16]

Treatment of endometriosis-associated pain

Patients with endometriosis may have different symptoms, but the most important one is the pain syndrome which is characterized by dysmenorrhea, pelvic pain, lower abdominal pain and dyspareunia. In some women the highly invasive ectopic endometrium, manifested as deep lesions, is responsible for the severe pain; however, the exact mechanism by which this clinical manifestation occurs is still unknown.

Specific types of pelvic pain are correlated with anatomic locations. Dysmenorrhea increases with Douglas pouch adhesions, dyspareunia with uterosacral ligament deep infiltrating endometriosis, lower urinary tract symptoms were more frequent when lesion involved the bladder, and gastrointestinal symptoms were associated with bowel or vaginal deep lesions.[17]

The main purpose of the current medical treatment of endometriosis is to create an amenorrheic state, in other words, to create a hypoestrogenic environment by suppressing estrogen secretion of the ovary (GnRH agonists and antagonists), inducing a pseudopregnancy (progestins) or by local estrogenic inhibition of the ectopic endometrium (progestins, androgenic progestins). However, therapy involves diverse collateral manifestations like alterations in the bone density or androgenization symptoms such as the coarsening of the voice, clitoris hypertrophy, seborrhoea, acne, hirsutism, dyslipemias in the case of danazol, a decrease in libido, vaginal dryness, and an increased body temperature with the use of GnRHa.[18]

Hormonal treatment of clinically diagnosed endometriosis includes the use of analgesic and antiprostaglandin agents such as nonsteroideal anti-inflammatory drugs (NSAIDs); however, the physician should determine when a dose is no longer adequate and to proceed to the next line of therapy, which typically includes combination estrogen/progestin oral contraceptives, progestins, or suppressors of estrogen production such a danazol. Psychotropic drugs have also been used in the management of chronic pelvic pain; however, such use requires caution and administration by an appropriate medical specialist, as well as a workup to rule out other causes of the pain.

First line of medical treatment for chronic pelvic pain is usually acetaminophen or aspirin. Second line of therapy are NSAIDs, which inhibit prostaglandin synthesis and thus, are most effective when administered prior to onset of symptoms. To avoid their serious side effects, a new generation of NSAIDs has been introduced that specifically inhibits cyclooxygenase-2. These drugs are not more effective for treating dysmenorrhea than naproxen or ibuprofen, but they have a much lower risk of gastric damage.

Combination estrogen/progestin oral contraceptives are often used initially for women with chronic pelvic pain who have an otherwise negative evaluation. Rationale for its use includes inhibition of ovulation and decrease in overall mean gonadotropin levels, decreased menstrual flow and, decidualization of implants, including decreased production of intracellular receptors.

Randomized clinical studies comparing the use of 2 or more drugs have also been performed, with interesting outcomes. Combined oral contraceptives have been compared to GnRH agonists for the treatment of endometriosis associated pain. In a study designed to achieve an 80% success in detecting a 35% difference on the observed effects, treatment using oral contraceptives ended up being significantly less effective than GnRH analogs used to reduce dysmenorrhea, and almost as effective for dyspareunia and unspecific pelvic pain. However, the adverse effects were more noticeable in patients treated with GnRHa.[18, 19]

Other studies compare the efficacy of GnRH agonists with the efficacy of add-back therapy during a 6 months treatment, concluding that during this period of time pain relief is similar to therapies that only use analogs.

In a published Cochrane study the effectiveness of GnRH analogs for the treatment of pain symptoms was determined by comparing it to a group without treatment (either placebo or surgical treatments). No mayor differences were found among the groups.[18]

Recent studies are introducing the use of

TABLE I.—*Different medical treatments assayed in endometriosis patients.*

— High doses of estrogens
— Pseudopregnancy (progestins)
— Combinations of estrogens plus progestins
— NSAIDs
— Antiprogestins (SMPRs)
— Pseudomenopause (danazol – GnRH analogs)
— Aromatase inhibitors
— Immunomodulators

aromatase inhibitors and selective progesterone receptor modulators (SPRMs) as the new medical treatment for endometriosis, as well as new anti-inflammatory drugs (tumor necrosis factor inhibitors, matrix metalloproteinase inhibitors, cyclooxygenase-2 inhibitors).

The use of aromatase inhibitors in patients with previously medically and surgically treated endometriosis, and who obtained unfavourable outcomes in previous treatments, showed a large reduction of endometriosic implants and pain in patients that were part of this study. According to this, aromatase inhibitors could be a candidate for the treatment of endometriosis.[20-22]

The SPRMs are a potential therapeutic concept in endometriosis. These SPRMs are defined as a new class of progesterone receptors and they exhibit both progesterone agonistic and antagonistic activities *in vivo*, showing high binding-affinity to progesterone receptor ligands. In the absence of progesterone they act as progestins, but when progesterone is present, they act as antiprogestins in some tissues, mainly in the endometrium. Studies with non-human primates show an antiproliferative effect in the endometrium. The exact mechanism by which this occurs is still unknown. However, 4 possible working hypothesis are believed to take place: i) blockage progesterone action in the functioning of the spiral arteries; ii) suppression of proliferative estrogenic effects; iii) regulation of estromal growth factors; iv) expression induction of androgenic factors in the endometrium.

These studies show that the SPRMs have a special selectivity over the estrogen-dependent endometrial growth and induce a reversible amenorrhea without systemic effects of androgenic deprivation. Because of all of these, SPRMs help relieve pain in patients with endometriosis.[23]

Table I shows differents medical treatments assayed in endometriosis patients.

Treatment of endometriosis related infertility

Although prevalence may vary among different studies and populations studied, endometriosis is found in 25% to 40% of all infertile women, compared to the 2% to 5% found in the overall population. Several lines of evidence suggested that some women may tolerate transplantation of autologous endometrial cells in to the peritoneal cavity. However, if we take this concept further by speculating that essentially all women have endometriosis, those with clinical sequelae represent a subset of women in whom transplanted endometrial cells are not effectively eradicated across menstrual cycles. An alternative view is that women with minimal and mild endometriosis are those who have not yet constructed a defense against their disease, allowing these endometrium transplants to coexist in the peritoneal milieu of the pelvis. These implants establish a blood supply and may transmit various biochemical signs, often discordant with those of the normal endometrium. Such biochemical message can be detected in the peritoneal fluid and may adversely affect fertility, although the mechanisms by which such infertility arise remains poorly understood.[24]

A wealth of publications proposed that the endometriosis and inflammation may have an unfavorable influence of infertility. A recent meta-analysis of assisted reproductive technologies demonstrated that, once confounding factors are controlled for, the pregnancy rate in women with endometriosis is approximately 50% of the rate of women with tubal factor infertility. Peritoneal fluid of women with endometriosis contains elevated amounts of macrophages and their secreted products, such a growth factors, cytokines and angiogenic factors. However, ad-

vanced stages of endometriosis may have easily understandable factors, such as distorsion of anatomy, causing infertility.[25]

Endocrine and ultrasound studies in women with minimal endometriosis suggest that ovulatory dysfunction contributes to their infertility. Abnormalities observed include reduced follicular growth rate, reduced preovulatory follicle functional capacity, impaired LH surge pattern and amplitude, reduced oocyte fertilizing ability and disturbed early luteal function. Luteal phase abnormalities include indistinct early luteal phase rises and basal temperature and delayed return to the low temperature phase at menstruation.

Preovulatory follicular function is estimated by steroid measurements in follicular fluid (FF) and by determining granulosa cell steroidogenic capacity when collected at oocyte recovery for *in vitro* fertilization (IVF). Reduced LH concentration in FF was associated with impaired fertilization on oocytes *in vitro*, despite normal FF FSH and steroid levels.[26, 27]

In contrast to above studies, another group of investigators found significant, apparently favourable, increases in FF progesterone and decreases in testosterone concentration in patients with endometriosis, together with increased granulosa cell steroidogenesis.

When considering drug treatment to improve fertility, several medications have been used depending on the type of treatment considered and the diagnosis. But before introducing these publications, we have to remember that evaluating the effect of a drug to improve fertility in a certain population has some intrinsic difficulties, basically that 50% of the population will conceive spontaneously, and also patient heterogeneity, which makes evaluation a difficult task.[28-32]

Ovulation induction seems to be beneficial to most of these patients. In women with stages I-II endometriosis, the use of clomiphene citrate for ovulation stimulation resulted in a higher pregnancy rate than the use of danazol for ovarian suppresion (OR = 2.9, 95% CI 1.2 – 7.1 *vs* 1.02, 0.5-2.3). One non-randomized study examined pregnancy rate after expectant management, clomiphene citrate or HMG following surgical treatment for endometriosis. In this study, pregnancy rate for expectant management, clomiphene citrate and HMG were 0.021, 0.066 and 0.174 respectively (expectant *vs* HMG P = 0.005).

These studies suggest some improvement infertility from ovulation induction. In systematic reviews of the role of ovulation induction and/or intrauterine insemination in unexplained infertility, most trials reported in favour of the use of clomiphene citrate.

Treatment with intrauterine insemination (IUI) improved fertility in minimal-mild endometriosis: IUI with ovarian stimulation is effective but the role of unstimulatied IUI is still uncertain.[33-35]

Assisted reproductive technologies, in particular IVF, theoretically should maximize fertility rates by removing gametes and zygotes from the hostile peritoneal environment and bypassing abnormal pelvic anatomy associated with endometriosis. It has been shown that IVF is a successful treatment for endometriosis-related infertility, although pregnancy rates are reduced by half when compared to non-endometriosis patients; similarly, pregnancy rates are almost double in minimal-mild stages compared to moderate-severe stages.[36-39]

GnRHa are used in IVF treatments to prevent a premature rise in LH levels. Retrospective studies have shown that endometriosis patients show a better cycle outcome when GnRHa were used, so this led to the hypothesis that precycle treatment with GnRHa might improve IVF results in these patients. Two randomized trials have shown promising results with 3 or 6 months of GnRHa treatment prior to IVF, although the studies are underpowered to extract definitive conclusions.[40, 41]

Conclusions

Medical treatment of endometriosis symptoms is still a matter of intense research as currently available drugs are far form being the perfect treatment. The ideal drug, without side effects, for the treatment of endometriosis

that eases the pain and improves fertility without inhibiting ovulation and menstruation, has not been found yet. However the use of immunomodulators is a promising new alternative. So far, medical treatment is moderately effective in reducing pain but ineffective improving fertility; a combination of medical treatment with assisted reproductive technology (ART) may be beneficial.

Riassunto

Trattamento medico dell'endometriosi

Il trattamento medico dell'endometriosi è un aspetto critico dell'approccio terapeutico a questa patologia. Questa lavoro presenterà una revisione della letteratura corrente sul trattamento medico dell'endometriosi, senza ricorso al trattamento chirurgico o a una combinazione tra i due.

L'obiettivo principale dell'attuale trattamento medico dell'endometriosi è di creare uno stato amenorroico, in altre parole di creare un ambiente ipoestrogenico sopprimendo la secrezione di estrogeni dall'ovaio. Le ricerche attuali si sono focalizzate sullo sviluppo e mantenimento dell'endometriosi. Questo comprende i modulatori dei recettori per il progesterone, gli analoghi dell'ormone liberante la gonadotropina (GnRH), gli inibitori della aromatasi e gli inibitori del tumor necrosis factor α, gli inibitori dell'angiogenesi, gli inibitori della matrice metallo-proteinasi e gli agonisti del recettore β per gli estrogeni quali gli immunomodulatori. Questi farmaci riducono la disseminazione delle lesioni e riducono i sintomi correlati alla patologia.

Il trattamento medico è moderatamente efficace nel ridurre il dolore ma inefficace nel migliorare la fertilità; una combinazione del trattamento medico con le tecniche di fecondazione assistita possono essere di beneficio nel migliorare la fertilità.

Parole chiave: Endometirosi, terapia - Dolore pelvico - Infertilità.

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