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Medical therapy for endometriosis: a literature review

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Abstract

Background

Endometriosis is a chronic and complex disease, originated by the presence of endometrium outside uterine cavity, such as ovaries, fallopian tubes, peritoneum, vagina, intestines. The main symptoms are related to internal bleeding and chronic inflammation causing dysmenorrhea, chronic pelvic pain, dyspareunia and dysuria. Owing to adhesions, endometriosis leads to infertility. Although endometrial cells are in abnormal sites, they are influenced as well by hormonal changes and respond in a similar way to the cells developed inside the uterus.

Objectives

To determine the actual role of medical therapy in the treatment of endometriosis.

Search strategy.

We performed a systematic review of publications from 1984 to January 2015 via PubMed search, regarding medical therapy on endometriosis. Additional relevant articles were identified from citations within these publications.

Main results.

Among various hormonal drugs for endometriosis the most used are: Gonadotropin Releasing Hormone (GnRH) agonists, Oral Contraceptives (OCP), danazol, aromatase inhibitors and progesterone with its derivatives. GnRH agonists (GnRHa) increase the levels of GnRH inducing a down-regulation and hypoestrogenism. Main side effects are unpleasant menopausal inducted symptoms: flushing and osteoporosis. OCP reduce the production of gonadal estrogen by means of a negative feedback mechanism. A part from reducing estrogens, they interfere with the production of prostaglandins giving a favorable effect on both inflammation and pelvic pain. Danazol is a derivative of the synthetic 17α-ethinyltestosterone. It induces a hypoestrogenic-hyperandrogenic condition, which blocks endometriotic foci and clinical symptomatology. Its oral use is limited by several side effects as the following: weight gain, muscle cramps, acne, seborrhoea, decreased breast

dimension, hirsutism and tendency to the virile tone of the voice. Progestins have both a central and peripheral effect. They depress mitogenic action and estrogen production. The endometrium tends to secretory transformation, decidualization and atrophy. Several derivatives are used: medroxyprogesteron acetate (MPA), dydrogesterone, norethisterone, lynestrenol, desogestrel. In the last years, they have been used in many ways as oral, parenteral and indouterine (Levonorgestrel-intrauterine device or LNG-IUD) therapy. Nevertheless, the LNG-IUD is not approved for the treatment of endometriosis. The employ of progestins has been limited because of many side-effects among which breast tenderness, weight gain, acne, hirsutism and irregular bleeding. Recently dienogest, a selective progestin combining the pharmacologic properties of 19-norprogestins and progesterone derivatives gets a potent effect at the endometrium providing an efficient pain relief equivalent to GnRH agonists and reduces ectopic implants. Compared to other progestins and GnRH agonists, dienogest has been found more effective and better tolerated. Actually it remains an elective drug for medical treatment of symptomatic endometriosis.

Conclusions

Endometriosis remains a chronic troublesome disease, difficult to heal completely. It interferes on the quality of life, causing pain and infertility. The use of new drugs including new progestins allows a more suitable treatment and reduces need for surgery.

Keywords: Endometriosis, Medical therapy, Progestins, GnRH agonists, Dienogest

Keywords: Endometriosi, Terapia medica, Progestinici, GnRH-agonisti, Dienogest

Background

Endometriosis is a chronic and complex disease, originated by the presence of endometrium outside uterine cavity, such as ovaries, fallopian tubes, peritoneum, vagina, intestines. The main symptoms are related to internal bleeding and chronic inflammation causing dysmenorrhea, chronic pelvic pain, dyspareunia and dysuria. Owing to adhesions, endometriosis may lead to infertility. Infertility has been found to have a negative impact on women's quality of life and on the sex life of couples. Feelings of shame are often associated with infertility. It is easy to move from procedures that have failed to the feeling that "I am a failure". Shame is a painful feeling associated with faltering self-esteem, and a sense of inadequacy, helplessness and defectiveness. The internalization of unworthy or abusing parents (1) may also play a role in causing such emotion together with other dysfunctional attitudes (i.e. insecure attachment and problematic internet use) (2, 3) and disadaptive disorders (i.e. psychopathic traits) (4, 5). Thus, the modified concept "infertile woman" is considered differently from the head noun "woman" (6) causing a sort of stigmatization of the person not able to conceive.

Although endometrial cells are in abnormal sites, they are influenced as well by hormonal changes and respond in a similar way to the cells developed inside the uterus. To explain the origin of endometriosis, many theories has been proposed (7). The retrograde menstruation theory is the oldest hypothesis. It proposes that endometriosis is a consequence of retrograde flow of endometrial cells

which reach the pelvic cavity crossing fallopian tubes during menses.

The coelomic metaplasia theory postulates that endometriosis derives from specialized cells that are present in the mesothelium turning into endometrial tissue.

The hormonal theory plays a central role for endometriosis since it is typical of women in reproductive age and it decreases in post menopause because of physiologic hypoestrogenism. The Oxidative Stress and Inflammation theory derivates from the observation that reactive oxygen species (ROS) cause lipid peroxidation and lead to DNA damage in endometrial cells (7).

The theory of Immune Dysfunction explains the association between defective immune response and endometriosis. It is supported by the presence of a higher concentration of activated macrophages, decreased cellular immunity and repressed NK cell function (8). The apoptotic theory origins from the evidence that genes regulating the apoptosis pathway in ectopic endometrial cells have an important function in spreading the disease. In addition the inhibition of the apoptosis may be mediated by the transcriptional activation of genes that usually promotes the inflammatory and proliferative mechanism (9).

Genetic theory is suggested by the common observation of familiarity of endometriosis. By means of laser capture microdissection and high resolution comparative genomic hybridization (CGH) arrays, several genomic alterations in endometria have been found (10).

Moreover the regeneration of the endometrium after menstruation, delivery or surgical curettage, supports the theory of stem cells.

Endometriosis is classified as minimal, mild, moderate, or severe based upon visual observations at laparoscopy. Minimal disease is characterized by isolated implants and no significant adhesions. Mild endometriosis consists of superficial implants less than 5 cm in aggregate without significant adhesions. In moderate disease, multiple implants and scarring (adhesion) around the tubes and ovaries may be evident. Severe disease is characterized by multiple implants, including large ovarian endometriomas along with thick adhesions. The medical treatment of endometriosis requires mainly hormonal therapy and non steroidal anti-inflammatory drugs (NSAIDs). Aim of this report is to determine the actual role of medical therapy in the treatment of endometriosis.

Materials and methods

We performed a systematic review of publications from 1984 to January 2015 via PubMed search. Additional relevant articles were identified from citations within these publications.

Results

Among various hormonal drugs for endometriosis the most used are: GnRH-a, Oral contraceptives

(OCP), danazol, aromatase inhibitors and progesterone with its derivatives.

GnRH-a increase the levels of GnRH inducing a down-regulation and hypoestrogenism. Side effects are unpleasant menopausal inducted symptoms as for as flushing and osteoporosis (11). GnRH and its analogs have been extensively used in clinical medicine since they were synthesized in 1971. Native GnRH stimulates gonadotrophs of the anterior hypophysis and has been used for induction of ovulation. The GnRH-a are more potent and have got a longer half-life than native GnRH. They produce an initial stimulation of pituitary gonadotropins that results in secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and the expected gonadal response. This mechanism is followed by down-regulation and inhibition of the pituitary-gonadal axis. GnRH-a therapy decrease production of the hormone estrogen to the levels women have in post-menopausal age. This effect stops menstruation and reduces the size of endometriosis. GnRH-a have been used by nasal spray or depot injection. The usual dosage ranges between 400 to 800 milligrams for nasal naferelin, 3.6 and 3.75 milligrams for monthly subcutaneous goserelin and, respectively, leuprorelin and, finally, 11.25 milligrams for every three monthly parenteral administration. Side effects comprehend vaginal dryness, hot flashes, lowering of libido, breast tenderness, depression, headaches and irregular bleeding. When treatment last for 6 months or more, a reduction of bone calcium is observed. Hypoestrogenic side effects and bone loss are prevented by “add-back” therapy with norethindrone (10 mg daily) or the daily combination of low dose norethindrone (2.5 mg), sodium etidronate (400 mg), and calcium carbonate (500 mg). Recurrence rates over 5 years range from 37 to 74% depending on severity of endometriosis. The benefits of treatment may be temporary or definitive. GnRH-a therapy is widely used to shrink endometriosis implants, which causes pain. It is a first or a second-choice treatment that is used when several months of birth control pill therapy have not been effective. GnRH-a therapy is sometimes used before surgery to make implants easier to remove. This can help reduce the amount of scar tissue created by the surgery (12). Besides, estrogen receptor (ER) ligands, chloroindazole (CLI) and oxabicycloheptene sulfonate (OBHS), have been found showing a strong ER-dependent anti-inflammatory activity in a preclinical model of endometriosis that recapitulates the estrogen dependence and inflammatory responses of the disease in immuno-competent mice and in primary human endometriotic stromal cells in culture. Estrogen-dependent phenomena, including cell proliferation, cyst formation, vascularization, and lesion growth, were all arrested by CLI or OBHS, which prevented lesion expansion and also elicited regression of established lesions, suppressed inflammation, angiogenesis, and neurogenesis in the lesions, and interrupted crosstalk between lesion cells and infiltrating macrophages. Studies in ERα or ERβ knockout mice indicated that ERα is the major mediator of OBHS effectiveness and ERβ is dominant in CLI actions, implying involvement of both ERs in endometriosis. Neither ligand altered estrous cycling or fertility at doses that were effective for suppression of endometriosis. Hence, CLI and OBHS are able to restrain endometriosis by dual suppression of the estrogen-inflammatory axis. These compounds have the desired characteristics of preventive and therapeutic agents for clinical endometriosis and possibly other estrogen-driven and inflammation-promoted disorders (13).

Oral contraceptives (OCP) reduce the production of gonadal estrogen by means of a negative feedback mechanism. A part from reducing estrogens, they interfere with the production of

prostaglandins giving a positive effect on both inflammation and pelvic pain (14). OCP or birth control pills help make menstruations lighter, more regular, and shorter. Women prescribed contraceptives also report relief from pelvic pain. In general, the therapy contains two hormones-estrogen and progestin, a progesterone-like hormone. Women who can't take estrogen because of cardiovascular disease or a high risk of blood clots may use progestin-only pills. The administration is for 21 with 7 days of interval or continuously, stopping menstrual period. Pain relief usually lasts only while taking the pills, while the endometriosis is going to be suppressed. When treatment stops, the symptoms of endometriosis may come back (along with the risk of sterility). In the event of severe endometriosis women may continue treatment indefinitely. Occasionally, some women have no pain for several years after stopping treatment (15).

Danazol is a derivative of the synthetic 17α-ethinyltestosterone. It induces a hypoestrogenic-hyperandrogenic condition, which blocks endometriotic foci and clinical symptomatology. Its oral use is limited by several side effects as the following: weight gain, muscle cramps, acne, seborrhoea, decreased breast dimension, hirsutism, and tendency to the virile tone of the voice. There was no statistically significant difference between GnRH-a and danazol for dysmenorrhoea RR 0.98 (95% CI 0.92 to 1.04; P = 0.53). This equates to 3 fewer women per 1000 (95% CI 12 to 6) with symptomatic pain relief in the GnRH-a group. More adverse events were reported in the GnRHa group. There was a benefit in overall resolution for GnRH-a RR1.10 (95% CI 1.01 to 1.21, P=0.03) compared with danazol. There was no statistically significant difference in overall pain between GnRH-a and levonorgestrel SMD –0.25 (95% CI –0.60 to 0.10, P=0.46). Evidence was limited on optimal dosage or duration of treatment for GnRH-a. No route of administration appeared superior to another (16, 17).

Progestins have both a central and peripheral effect. They depress mitogenic action and estrogen production. The endometrium tends to secretory transformation, decidualization and atrophy (18). Several derivatives are used: medroxyprogesteron acetate (MPA), dydrogesterone, norethisterone, lynestrenol, desogestrel. In the last years, they have been used in many ways as oral, parenteral and indouterine (Levonorgestrel-intrauterine device or LNG-IUD) therapy. Nevertheless, the LNG-IUD is not approved for the treatment of endometriosis. When administered continuously, progestins are effective for the management of pain and other symptoms of endometriosis, with beneficial effects for both amenorrhea and anovulation. Certain progestins are effective for endometriosis only at high doses when compared with use for other indications, which may increase the likelihood of adverse events, elevating the risk of cardiovascular adverse complications (19, 20). The employ of progestins have been limited because of many side-effects among which breast tenderness, weight gain, acne, hirsutism and irregular bleeding (21, 22).

Recentely Dienogest, a selective progestin combining the pharmacologic properties of 19-norprogestins and progesterone derivatives gets a potent effect at the endometrium providing an efficient pain relief equivalent to GnRHa and reduces ectopic implants. According other progestins and GnRH-a, Dienogest has been found more effective and better tolerated. Regarding the effect of dienogest on pelvic pain, the mean VAS score was found significantly decreased to 11.52 (±11.26)

mm at the end of the extension study in the total population (9.72 ± 7.44 mm in the prior-dienogest group and 13.49 ± 14.14 mm in the prior-placebo group). The mean VAS score was statistically significantly reduced by 43.2 (±21.7) mm over the total treatment period of 65 weeks (i.e., the placebo-controlled plus extension study; $P < 0.001$). Continued dienogest treatment is associated with a progressive reduction in the number of bleeding/spotting days, number of bleeding/spotting episodes and duration of bleeding/spotting episodes between 90-day reference periods. Besides, laboratory parameters, vital signs and body weight remained stable or underwent minimal changes during the treatment. Actually it remains an elective drug for medical treatment of symptomatic endometriosis (23). Dienogest has also been found to lead to improvement of urinary symptoms caused by bladder endometriosis for patients who refuse surgery (24, 25).

Concerning sterility, if pregnancy does not occur after laparoscopic treatment, *in vitro* fertilization (IVF) may be the best option to improve fertility. Taking any other hormonal therapy usually used for endometriosis-associated pain will only suppress ovulation and delay pregnancy. Performing another laparoscopy is not the preferred approach to improving fertility unless symptoms of pain prevent undergoing IVF. Multiple surgeries, especially those that remove cysts from the ovaries, may reduce ovarian function and hamper the success of IVF. Regarding aromatase inhibitors (A.I.) for endometriosis, actually, the treatment of endometriosis is still experimental, because the results are not definitive. Aromatase is a protein in the body that is responsible for producing oestrogens. It is found in ovaries, skin and fat. Aromatase is represented in high levels in the ectopic endometrial tissue of women with endometriosis, interfering with the growth of disease. By giving women A.I. the growth of endometriosis and the associated inflammation tend to reduce. A.I. used for endometriosis include letrozole and anastrozole. If used alone, they may stimulate the ovaries and develop ovarian cysts. The other drugs associated may be oral contraceptive pill, progestogens or a GnRH-a. The most common side effects are mild hot flushes and decreased libido. However, A.I. markedly reduce the pelvic pain in most women (26–28). Regarding NSAIDs, the comparison with placebo shows no evidence of positive effect on pain relief [odds ratio (OR) 3.27, 95% CI 0.61 to 17.69] in women with endometriosis. There was also inconclusive evidence to indicate whether women taking NSAIDs (naproxen) were less likely to require additional analgesia (OR 0.12, 95% CI 0.01 to 1.29) or experience side effects (OR 0.46, 95% CI 0.09 to 2.47) when compared to placebo. There is inconclusive evidence to show whether NSAIDs (naproxen) are effective in managing pain caused by endometriosis. There is no evidence to show whether any individual NSAID is more effective than another (29).

Conclusions

Endometriosis remains a chronic troublesome disease difficult to heal completely. It interferes on the quality of life, causing pain and infertility. New therapies offer relief from pain, prevent progression of the disease, and improve fertility avoiding in some cases the suitable recourse to stimulation and *in vitro* fertilization (30–33). The use of new drugs including new progestins allows a more appropriate treatment and reduces need for surgery (34). Finally, it is important, during both the

diagnostic and the treatment process, to check the most evident symptoms (overt symptoms) as well as the most hidden (covert symptoms), thus taking care of the patient's quality of life as well (35–39).

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