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Current Drug Therapy Recommendations for the Treatment of Endometriosis

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Contents

Abstract

The principal symptoms and signs of endometriosis are tissue lesions and pelvic pain. These occur to varying degrees, with a chronic pattern and a tendency for deterioration with time. Patients with endometriosis often also have fertility problems, but the relationship between this and the signs and symptoms of the disease is inconsequent; the basic pathophysiology is not exactly known. Although an immunological defect resulting in an inflammatory reaction around discharged menstrual debris in the pelvic cavity has been shown, no treatments based on this process are available.

Estrogen often plays an important role in the progression of lesions and pain. Therefore, the aim of treatment usually has been to downregulate the ovaries and/or give antiestrogenic drugs as an alternative to surgical removal. As complete downregulation of the ovaries and hypoestrogenaemia does not seem to be crucial, achievement of amenorrhoea seems to be sufficient. This means that women may continue to have circulating estrogen levels so that severe hypoestrogenic adverse effects such as bone demineralisation, dry vagina, psychiatric symptoms or anabolic/androgenic effects of gestagens can be avoided. However,

as both symptoms and the dependence of hormones may vary between and within women, the treatment needs to be individualised.

There are a number of available treatments for endometriosis on the market and it is important for the doctor to know how to reach the therapeutic window of these treatments for each woman. It is also important to inform the patient about the different possibilities so that the treatment with the least impact on her quality of life can be chosen. When the therapeutic window has been identified, the treatment may then either be continued for a long period of time or be repeated when needed.

1. Lesions and Pelvic Pain – Two of the Signs of Endometriosis

Endometriosis is regarded as a chronic disease, and as such it may present itself in an unlimited number of ways – from acute, shortlived symptoms, to chronic symptoms which persist for decades. The major symptom is pain, which in the early phases of the disease, and sometimes for years afterwards, is cyclic and is usually related to menstrual bleedings. In time, however, these painful periods become more prolonged and the pain becomes more acyclic, turning into a chronic pain syndrome. The pains usually do not disappear spontaneously, only during pregnancy and after the menopause.

However, there are also cases with advanced lesions causing tissue destruction and adhesions, but without any symptoms.[1] In a prospective study of 86 women who underwent laparoscopy for other indications and had no symptoms typical of endometriosis, 45.3% were found to have macroscopic lesions: 32.5% stage I (minimal) according to the American Fertility Society (AFS) classification, 9.3% stage II, 1.1% stage III and 2.3% stage IV, i.e. advanced endometriosis.[2] Placebo-controlled studies have shown that about 7% of asymptomatic women with visible lesions will have symptoms within 6 months. The findings of extensive, but painless endometriosis, have led to discussions regarding the definition of the disease.[3,4] Does the disease consist only of endometriotic lesions, and if so which kind of lesions and how extensive, or of the pain symptoms, the combination of both or basically something different? Superficial lesions are common in asymptomatic women, and some authors have questioned whether this represents a disease, or rather an expression of a normal physiological change.[5-7] However, the occurrence of pain and visible endometriotic lesions are probably only 2 of the signs of the disease. As the lesions often cause pain, the treatment of the combined syndrome of lesions and pain is widely accepted. However, the occurrence of visible lesions without pain, or the occurrence of pelvic pain without visible endometriotic lesions (or other pathology), is a more debated indication for hormonal treatment.

2. Development of Endometriotic Lesions

Sedimentation, adhesion and implantation of endometrial cells that gain access to other parts of the body than the uterine cavity, mainly the pelvic cavity, is usually regarded as the cause of the disease. Normally, such fragments are cleaned away by immune cells but in women developing endometriosis they are not; this is a result of an immunological defect. These endometrial cells, allowed to remain in a new location, give rise to an inflammatory reaction.[8] During this acute phase of inflammation, a cascade of inflammatory products are released, which, in different ways, cause pain. However, in these early stages, the implants are hardly visible on laparoscopy.[9] Thus, a diagnostic laparoscopy at this phase might not give an explanation for the pain. A vascular proliferation manifested as a result of the inflammation might be disregarded. However, if the cause of inflammation, i.e. the menstrual debris, is not exposed to the pelvic surfaces any more, the inflammation, and there-

fore the pain, will usually disappear. At this stage amenorrhoea often will cause pain relief. These fresh tissue fragments retain a hormonal sensitivity similar to that of the endometrium, and may proliferate or disappear according to hormonal exposure and sensitivity. On the other hand, surgical extirpation of minor endometriotic lesions will give only temporary symptomatic relief as new menstrual debris will start the process again.

In time, a chronic healing phase and reorganisation of the lesions takes place, resulting in a varying degree of fibrosis surrounding and growing into the endometriotic tissue, resulting in less exposition of the ectopic endometrium to inflammatory cells, thus the release of biochemical pain-producing substances is reduced. However, this fibrosis also may cause a tissue deformation, which may cause another, more persistent, type of pain. This stage of endometriosis is less sensitive to hormonal influence, as the connective tissue is not hormonally regulated. It also appears that the steroid receptor status is different in primary lesions compared to recurrent or reactivated lesions.[10] This might depend on an influence on the receptor levels of other inflammatory and growth regulating factors. The estrogen and progesterone receptor levels are also different between lesions in different localisations, probably because of paracrine influences. Therefore the effect of hormonal treatment is less pronounced in some cases and is sometimes absent. Parallel to the changes of some lesions into fibrotic lesions, new lesions will appear as long as a retrograde menstruation takes place. Thus the effect of treatment in an individual case is not possible to forecast, as both an acute and a chronic inflammatory process are ongoing in parallel in varying proportions in each case at a certain time.

3. Development of Pelvic Pain

Endometriotic pain initially has the character of intense dysmenorrhoea and later other forms of pain appear as dyspareunia and/or pelvic pain, not related to menstruation or sexual intercourse, but being more or less continuous. The pain pattern is different also depending on type, location and stage of the lesion.[11-14] There is little basic research on endometriotic pain and pathophysiological connections between endometriotic lesions and pain.[15]

4. Diagnosis and Goals of Treatment

The only diagnostic tool so far is the eye. Visual diagnosis at gynaecological examination or surgery is usually enough, but if there are any doubts, histological examination of lesions is required. Ultrasound examination may give indication of an endometriotic cyst, but is not sufficient to diagnose minor lesions. Magnetic resonance imaging has the same limitations.

The aim of treatment is to eliminate symptoms, reduce the process of inflammation and limit the tissue destruction that might result from longstanding disease. The primary aims are not always to delete the lesions *per se*, but to reduce the menstrual discharge that is estrogen-regulated, in that estrogen causes menstrual bleeding and proliferation of the discharged endometrial fragments. However, although the disease, defined as lesions and/or pain, may disappear for long periods after treatment, no definite cure is available, either pharmacological or surgical. Although endometriosis is regarded as related to retrograde menstruation, not even extirpation of the uterus and both ovaries can guarantee cure once the disease has become established.[16-17] The chronic inflammatory process is regulated by mechanisms other than retrograde menstruation, but may retain some estrogen sensitivity, which is why it can recur, e.g. if estrogen replacement therapy is given after the menopause.

The pharmacological therapeutic approaches available focus on endometriosis symptoms, mainly by suppressing the menstrual cycle and thereby removing the stimulatory effect of estrogen and menstrual debris. A favourable effect on pain is usually obtained within 1 or 2 months of ovarian downregulation. A complete downregulation is usually obtained by gonadotrophin-releasing hormone (GnRH) agonists, and continuous treatment with gestagens usually has similar effects. Recurrence

Table I. Placebo-controlled studies on the effect of treatment of endometriosis with gonadotrophin-releasing hormone agonists with or without add back. The treatment duration was 6 months in all studies

References	GnRH-agonist	Add-back	Placebo
Dlugi et al.[22]	Leuprorelin (n = 28)		n = 24
Eldred et al.[23]	Nafarelin (n = 94)	NET 0.7mg (n = 24)	n = 24
		or NET 1.4mg (n = 23)	
		or NET 2.45mg (n = 23)	
Kiilholma et al.[24]	Goserelin (n = 88)	Estradiol 2mg + NET 1mg (n = 43)	n = 45
Mukherjee et al.[25]	Leuprorelin (n = 28)	Etidronic acid (n = 15)	n = 13
Hornstein et al.[19]	Nafarelin (n = 49)		n = 44
Bergqvist et al.[27]	Triptorelin (n = 24)		n = 25
Hornstein et al.[26]	Leuprorelin (n = 201)	NET 5mg (n = 55)	n = 51
		or NET 5mg + conjugated estrogens 0.625mg (n = 47)	
		or NET 5mg + conjugated estrogens 1.25mg (n = 48)	

NET = norethisterone.

might occur at any time, and the recurrence rate of symptoms after treatment is high, 53% after 5 years.[18] However, downregulation of the ovaries seems to delay recurrences to some extent and as with other chronic diseases, some patients have symptoms of the disease only during a certain period of their lives. The duration until recurrence of symptoms is longer after GnRH agonist treatment than after placebo, whether hormonal treatment is preceded by surgical treatment or not.[19]

5. Gonadotrophin-Releasing Hormone Agonists

Several studies on the clinical effect of GnRH agonists on endometriosis have been published and their efficacy is comparable to those of previously established hormonal treatments.[20-21] Only 3 placebo-controlled studies on GnRH agonists without addback have been published (table I), all showing a significant effect of active treatment. We found that when triptorelin was compared with placebo during a 6-month treatment period, the active treatment resulted in a significantly greater reduction of not only dysmenorrhoea, but also pelvic pain and dyspareunia.[27]

GnRH agonists were developed for medical castration of elderly men with prostate cancer. Later it was realised that these agents might be suitable also for women with hormonal diseases. However, on the basis of pharmacodynamic and pharmacokinetic results already obtained in men, the same doses were used also in women with benign diseases. Several studies have shown a good effect on endometriosis but at the price of severe adverse effects. Most tissues have estrogen receptors and hypoestrogenic adverse effects appear both early during the treatment (vasomotor symptoms and mood changes) and in the long term (increased bone metabolism, resulting in reduced bone mass). Several studies on bone mass during GnRH agonist treatment have shown an increased bone turnover and a loss of 5 to 6% during 6 months of treatment.[25-26] This is within the normal range of physiological differences and women with endometriosis do not seem to have a lower bone mass than age-matched controls.[27] The bone loss is similar to the loss during breastfeeding i.e. 3 to 6% after 6 months.[28-29] The bone loss after 1 year of complete ovarian downregulation before the menopause has not been studied, but is probably similar to the changes after surgical oophorectomy, i.e. 10.7%.[30] There does not seem to be any difference in bone loss after natural compared with surgical menopause.[31] Most studies have shown a complete, or near-complete recovery of bone mass 6 months after the end of a 6-month period of ovarian downregulation.[32] Thus, a 6-month downregulation of the ovaries is

acceptable in most women.[33] However, women over the age of 40, who are spontaneously on a decreasing bone mass curve biologically, and women with other risk factors for bone demineralisation, such as smoking, should have their bone mass closely monitored and in certain cases they should be recommended an alternative treatment to GnRH agonists. One major problem is the fact that endometriosis is usually not a '6-month disease' and requires long term treatment.

Although the effect of GnRH agonists on serum lipids varies according to different reports,[34-37] no data are available so far concerning cardiovascular events related to treatment with GnRH agonists. This might not be a problem for short term treatment of 6 months' duration, but induction of a long term hypoestrogenic state would in fact result in progressively diminishing cardioprotection comparable to the postmenopausal period. Ovarian downregulation before the menopause also affects testosterone synthesis. After 2 months treatment with goserelin the mean serum testosterone level in women with endometriosis decreased by 50%.[38]

Different GnRH agonists with various administration routes are available, each one with its own specific advantages and disadvantages[24] (table II). Depot formulations given monthly or every third month are very convenient, as the intervals between doses are long and thus take a minimum of time and attention and the woman is not reminded daily of her disease. Depot injections also have very few local adverse effects. In some cases goserelin gives a small local bruise or itching and the injection of triptorelin can give a short sensation of local pain. Also daily subcutaneous injections (buserelin) are on the market, but these are hardly ever used for long term treatment. GnRH agonists given intranasally have usually to be repeated during the day i.e. nafarelin twice daily and buserelin 3 times daily. Besides causing some local adverse effects like irritation, pain or soreness in the nose, the administration schedule has to be remembered by the patient, who is reminded of her disease more than once a day.

Table II. Different gonadotrophin-releasing hormone agonists used for treatment of endometriosis

Substance	Route of administration	Administration intervals
Buserelin	Intranasal, subcutaneous	8 hours/1 day/28 days/3 months
Goserelin	Subcutaneous	28 days
Leuprorelin	Subcutaneous	28 days/3 months
Nafarelin	Intranasal	12 hours
Triptorelin	Intramuscular	28 days

Studies on different GnRH agonists have shown comparable results, but no prospective studies comparing 2 or more GnRH agonists have been published. When we compared goserelin and nafarelin in a large prospective Scandinavian multicentre study, we did not find any significant differences in effect on endometriosis symptoms or in hypoestrogenic adverse effects (Bergqvist, unpublished observations). Not surprisingly, nasal symptoms were most common in the nafarelin-treated group, but these were not uncommon in the goserelin-treated group.

However, other aspects can be put forward regarding the different types of formulations. The depot formulations usually cause a complete downregulation of the ovaries, and the effect cannot usually be modulated. They have to be administered every 28 days, although 3-month depots have recently become available. Thus, once the injection is given the patient is bound to the effects of the drug for a specified period of time and cannot change or inhibit it. The amenorrhoea resulting from a depot injection will often persist for up to 6 to 8 weeks, at least when the treatment has been given for some months. In patients experiencing many adverse effects, the intervals between administrations can, at the discretion of the physician, be extended by days or weeks. However, no controlled studies have been published to clarify in which cases and to what extent the injections may be spaced. Daily nasal administration allows greater individualisation of dosage. For example, in Scandinavia the standard dose of nafarelin is 200μg twice daily but in the US it is 400μg twice daily. Comparative studies on low dose treatment with 200μg daily have been published, showing accept-

able efficacy in many cases.[39-41] This has now resulted in a new concept for GnRH agonist treatment using a varying, stepdown or even patient-determined daily dose regimen (studies are ongoing). A flexible treatment schedule, similar to those for people with other chronic diseases as diabetes, rheumatism, allergy etc., allows a more biological adjustment of the dose according to the actual activity of the disease and individual metabolism.

There is a pathophysiological basis for this approach, namely that endometriosis often has a course that can vary according to many factors such as stress, immunological status, nutrition, endocrinological status, inflammatory diseases, other drugs and general wellbeing and the metabolism of given drugs varies between individuals. The aim of pharmacological treatment should be to assist the normal biological system to defend against pathological processes without causing other adverse effects negative for the life quality of the patient. For example, a complete downregulation of the ovaries results in a generalised hypoestrogenic status, involving most tissues like the skeleton, muscles, connective tissue, mucous membranes and the cardiovascular system. Symptoms usually appear to some degree within a few weeks and are reversible after up to 6 months of treatment. However, they might be serious and irreversible in the long term, i.e. after several months or years of treatment.

In 1992 Barbieri[42] presented the obvious but never previously clearly formulated idea of a therapeutic window. Different tissues have different sensitivity to/dependence on estrogen, with the endometrium and endometriotic tissue requiring high levels of estrogen for proliferation, while bone and vaginal mucus have the capacity to be intact on rather low levels of estrogen. Thus, if we can identify in every individual which estrogen level causes a downregulation of the endometrium and endometriotic tissue without interference with bone mass, muscles, connective tissue and mucus, then the treatment can be optimised. Such a moderate reduction of estrogen stimulation should not be deleterious to other tissues, thus offering the possibility of continuing treatment for a long, and possibly unlimited, period of time. Such titration can be made using nasal formulations, which allow the daily dose to be tailored. Although the therapeutic window usually is at a plasma estrogen level of 30 to 45 pg/ml, the window is individual, and assay of plasma levels of estrogen is usually not meaningful. It is more important to find out from the patient's symptoms and signs whether she is in her therapeutic window. Patient education is very important in order to obtain optimal treatment results. If the woman knows what the disease is about, how it can develop in the long run, and the pharmacological mechanisms of medicaments available, she is often the best person to decide which step will be the best for her in her specific situation. Moreover, such knowledge and a positive mentorship from the physician usually reduces her fear and anxiety, which is an important component in the pain experience. To define the therapeutic window is a collaborative work between the doctor and the patient.

6. Add-Back Therapy

In many cases it is not possible to find out the individual dose of GnRH agonist needed to reach the therapeutic window. In these cases, the depot formulations are suitable to completely inactivate the ovaries and then a low dose of estrogen is given as add-back orally or transcutaneously to avoid the hypoestrogenic adverse effects. Thus, in these cases the titration has to be performed the other way round, and the goal is to find the estrogen dose that is optimal to prevent hypoestrogenic symptoms and adverse effects but low enough to avoid stimulating the endometrium and endometriotic tissue to proliferation and bleeding. In a placebo-controlled study of add-back therapy using 25μg estradiol patches during 6 months treatment with goserelin, the reduction in bone mass was less, although not significantly so, in the estrogen add-back group compared with placebo add-back.[26]

The choice of estrogen preparation seems to be of minor therapeutic importance. Conjugated estrogens 0.625mg, estradiol 2mg orally or estradiol 25 to 50μg transcutaneously is usually sufficient.[43]

The physician has to present the different alternatives to the patient and give suggestions, but it is the choice of the patient as to which drug is likely to give her the best quality of life. A low dose of unopposed estrogen may be given daily, but if a higher dose of estrogen is needed to prevent hypoestrogenic adverse effects, it has to be combined with gestagens. Otherwise the endometrium might proliferate, and even if it does not bleed, it might develop into adenomatous hyperplasia and premalignant changes may develop in the long run. Gestagen added to estrogen may be given daily or sequentially in a dose of medroxyprogesterone acetate (MPA) 2.5 to 10mg daily or norethisterone 0.2 to 1.2mg or 2mg daily.[42,44] For example, if the woman has adverse effects from the gestagen, it is usually enough if it is given intermittently for 2 weeks every 1 to 3 months. Add-back with gestagen only has also been used when estrogen add-back is less attractive[45] (table III). However, a concomitant dose of up to 10mg norethisterone daily did not eliminate the bone demineralisation caused by nafarelin treatment and addition of 15mg MPA to goserelin did not prevent bone loss.[37,46-47]

This kind of polypharmacy might appear illogical. Why give a GnRH agonist to downregulate the ovaries, and then give gestagens, as well as estrogen, when gestagens alone might be enough?

7. Gestagens

Gestagens are the oldest hormonal medicaments for endometriosis now in use.[48-49] Gestagens also suppress the gonadotrophins, but do not usually downregulate the ovaries to the same pronounced degree as do GnRH agonists.[50] In low doses, with insufficient downregulation, this might result in a disturbed proliferation of the endometrium and bleeding. However, the effect of gestagens is to a great extent a question of dosage, and most gestagens may be given within a wide range of doses (table IV). For example, MPA, which is the most extensively studied gestagen for treatment of endometriosis, may be given in a dose from 5 to 50mg daily orally or 150mg injected every 3 months.[55] Even an oral daily dose of 100mg has been studied.[50] In order to obtain sufficient ovarian downregulation and control of bleeding, a dose of at least 20 to 30mg daily is recommended initially. In a 3-arm prospective, randomised study comparing danazol 600mg daily, gestrinone 2.5mg twice a week and MPA 10mg daily, we found a significant effect on endometriosis in all 3 treatment arms, although ovarian suppression was not complete in the MPA- and the gestrinone-treated groups.[52] Although these 2 groups showed bleeding and spotting at a higher frequency than the danazol-treated women, this did not seem to be important for regression or healing of the lesions. The dose may be reduced after 1 to 2 months according to symptoms and adverse effects. Norethisterone is given in doses from 0.2 to 1.2mg daily and lynestrenol at 5mg daily. This monotherapy offers good possibilities to find the therapeutic window for an individual woman, and titration of the dosage can often be handled by the woman herself after good and careful instructions.

Gestagens also have a direct antiestrogenic effect on endometriotic tissue by binding to progesterone receptors. However, the gestagenic effects are not only antigonadotropic, but as progesterone receptors are common in most tissues, gestagen treatment may cause several direct anabolic and androgenic adverse effects such as weight gain, oedema, acne, seborrhoea, oily skin and, often more important, affective disturbances such as mood changes and depression. However, it has to be mentioned that in some cases gestagens have a stabilising and vitalising effect on the mood. The balance between sufficient effect on the endome-

Table III. Different steroids used for daily add-back during gonadotrophin-releasing hormone agonist treatment of endometriosis

Estradiol	25-50μg transcutaneously twice weekly
	1-2mg orally daily
Conjugated estrogens	0.625-1.25mg orally daily
Medroxyprogesterone acetate	5-15mg orally daily
	150mg intramuscularly every 3 months
Norethisterone	0.7-10mg orally daily

Table IV. Different gestagens used for treatment of endometriosis

Reference	Gestagen	Dosage	Duration of treatment
Bergqvist et al.[51]	Medroxyprogesterone acetate	5mg daily	6 months
Bergqvist et al.[27]	Medroxyprogesterone acetate	30mg daily	6 months
Teichmann et al.[52]	Medroxyprogesterone acetate	50mg daily	6 months
Telimaa et al.[53]	Medroxyprogesterone acetate	100mg daily	6 months
Vercellini et al.[54]	Medroxyprogesterone acetate	150mg/3 months	1 year
Bergqvist et al.[51]	Gestrinone	2.5mg twice weekly	6 months
Teichmann et al.[52]	Lynestrenol	10mg daily	6 months
Overton et al.[49]	Dydrogesterone	40 or 60mg daily	6 months

triosis symptoms and disturbing adverse effects of gestagen treatment might be difficult to achieve, which is why the instructions to the patient to tailor the dose herself according to her daily status is very important. To help the patient, it is important to have a doctor or nurse available when needed for telephone consultations. If the patient finds her therapeutic window, she can stay on the treatment for years if needed. The most serious long term adverse effects of gestagen treatment are on plasma lipid levels and the cardiovascular system, and these have to be taken into consideration when long term treatment, perhaps for a period of years, is needed.[53-54] In a prospective double-blind comparative study of nafarelin 400μg daily and MPA 30mg daily, we found no significant differences between groups concerning the quality of life, but both groups showed improved wellbeing during and 6 months after treatment than before treatment (Bergqvist et al., unpublished observations).

There are some prospective studies published comparing GnRH agonists and gestagens and no significant differences in effect on endometriosis symptoms have been shown. However, the spectrum of adverse effects is quite different, and from the physician's point of view it is often difficult to know which types of adverse effects are least troublesome for the patient. Patients themselves may have difficulties in knowing which type of treatment they would prefer, if they have the choice. As the therapeutic effect of GnRH agonists and gestagens does not differ significantly, a change from one type of hormonal treatment to another is possible and it is the duty of the physician to offer the patient the most suitable treatment.

8. Testosterone Derivatives

The ethisterone derivative danazol was introduced in the early 1970s for the treatment of endometriosis. It was shown to have multiple effects besides gonadal downregulation: inhibition of steroidogenic enzymes, binding to androgen, progesterone and corticoid receptors and binding to sex hormone binding globulin (SHBG), displacing testosterone and thereby having an antiestrogenic effect by increasing free levels of testosterone. Danazol was shown to be effective in the treatment of endometriosis in several studies and became the gold standard worldwide. However, no comparative studies were published, and when the GnRH agonists were introduced to the market, danazol was found to be no better, and sometimes even less effective, than the agonists.[56] Thus, the multiple mechanisms of action of danazol did not give better results in endometriosis treatment than other hormones given for ovarian downregulation. As it has adverse effects which are often seriously androgenic and anabolic, the use of danazol is now diminishing. However, a very low dose of danazol, 50mg daily, (the usual dose is 600 to 800mg daily), has been tried and showed a temporary relief of endometriosis-associated pain and menstrual blood loss, indicating that other more suitable therapeutic doses of the drug might be found.[57]

Gestrinone has milder androgenic activity, but nevertheless a dosage of 2.5mg twice weekly has been shown to be sufficient to at least downregulate the ovaries. The effect on endometriotic lesions and endometriosis-related pelvic pain seems to be comparable to that of GnRH agonists.[58] The drug

is well tolerated, but is associated with more bleeding than danazol.[51] Like gestagens, the costs are much lower than for danazol and GnRH agonists.

9. Combined Contraceptives

Combined contraceptives are the most commonly used downregulators of the ovaries, and although they contain estrogen, the gestagen component results in a thin endometrium and only sparse bleeding at the regular withdrawals. Contraceptives have shown a beneficial effect on endometriosis-related pain, at least during the first few years, when the acute inflammatory reaction dominates, but no controlled studies on the effect on lesions have been performed. If dysmenorrhoea persists during cyclic use of combined contraceptives, a continuous dosage may be more helpful. Some reports on the development of ovarian cysts during treatment with combined contraceptives have contributed to the theory that endometriomas might be a special form of endometriosis, different to other forms, for example peritoneal endometriosis.

10. Duration of Hormonal Treatment

There is no specific time limitation known for the duration of hormonal treatment, provided that the woman is kept within her therapeutic window. The standard treatment duration has been 6 months, as most clinical studies have used that definition of treatment duration. Shorter treatment duration has also been studied, showing a more varying effect.[59-60] No prospective longer term treatment studies have been performed, but there is a wide clinical experience of long term treatment with gestagens and cases treated with GnRH agonists for up to 37 months have been reported.[62] Studies of retreatment for 3 months with nafarelin have been published.[62-63] The bone loss was 0.56 to 2%, indicating about the same or somewhat lower rate of bone loss as during the first 6 months of treatment.

There are no convincing indications for hormonal treatment before surgical interventions already decided on, but treatment after the surgical approach is often valuable, at least when not all endometriotic tissue has been removed.

11. Prostaglandin Synthetase Inhibitors (PGSIs)

The activation of macrophages in the pelvis as part of the inflammatory reaction leads to a marked release of prostaglandins and other pain-provoking substances. Endoperoxides can directly irritate nerve endings.[62] Nonsteroidal anti-inflammatory drugs (NSAIDs) block prostaglandin production by blocking the action of cyclooxygenase. Inhibition of lipoxygenase reduces the production of leukotrienes. Finally, NSAIDs may promote the central release of endogenous opioids.[65] Treatment with NSAIDs gives significant pain relief in 72% of cases of primary dysmenorrhoea[66] and endometriosis.[67]

12. Infertility

An effect of hormonal treatment on infertility related to endometriosis has been reported extensively, although very few studies have been placebo-controlled with a primary aim to study the effect on fertility. Looking at properly performed studies, none has shown any significant effect, which is why hormonal treatment is not indicated for treatment of infertility, only for endometriosis-associated pain. When infertility and severe pain related to endometriosis coexist, hormonal treatment may be needed first to reduce the pain, with additional treatment for the infertility. The most successful treatment is *in vitro* fertilisation, and in women with endometriosis the take-home baby rate is as good as in women with infertility caused by tubal disease, although the fertilisation rate is lower.[68-69]

13. Extragenital Endometriosis

Endometriosis may be localised to any tissue structure in the body[70] and the development and hormonal regulation seems to be comparable to that in the pelvis. In some tissues like the bowel, pleura and scar tissue, the response to hormonal

treatment is often limited and surgery is often necessary.

14. Conclusions

The principal mechanisms for hormonal treatment of endometriosis seem to be ovarian suppression and amenorrhoea. A complete downregulation of the ovaries usually does not seem to be required. Several studies of different types of hormonal treatment have shown a satisfactory effect on endometriosis symptoms and lesions with doses that make the patient amenorrhoeic but with some remaining ovarian function. This approach has not been significantly less effective than complete ovarian suppression. An incomplete ovarian downregulation is bone preserving and the consequences for the cardiovascular system are minimal. Other adverse effects of high dose treatments should be taken into consideration, including direct steroidogenic adverse effects or hypoestrogenic adverse effects of gestagens or of GnRH agonists. The goal for hormonal treatment of endometriosis is to find the therapeutic window for the patient, with a low level of circulating estrogen, for cardiovascular protection and preserving bone mass, but giving the patient sufficient symptomatic relief with a minimum of adverse effects. As endometriosis is a chronic disease, often requiring repeated or long term treatment, these aspects are especially important. It is important to cooperate with the patient to find the therapeutic window and to be flexible both in the choice of treatment and in the treatment schedule. The goal of treatment should be the highest quality of life possible for each patient.

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