GnRH agonists

GnRH agonists induce a very low **estrogen** level by stopping the follicular growth in the **ovary** completely. GnRH agonists can be taken intranasal, or through subcutaneous injection as a depot working either one or three months. Some of the most common GnRH agonists are nafarelin, leuprolide, buserelin, goserelin and triptorelin. GnRH agonists have more side effects than oral contraceptives and progestagens and are more expensive.

The side effects of GnRH agonists are related to the low level of estrogens and are comparable to the consequences of the menopausal status. These so-called hypo-estrogenic symptoms are hot flushes and night sweats, vaginal dryness and related pain during intercourse, and influences on the mental health up to depressive feelings. In the long term GnRH agonists are associated with osteoporosis. To reduce these symptoms, clinicians are recommended to prescribe hormonal **add-back therapy** as soon as GnRH agonists are started. Hormonal add back means adding a combination of estrogens and **progesterone** (oral contraceptives). This add back therapy takes away the side effects while the therapeutic effect is maintained. Since adolescents and young women up to the age of 23 have not reached their optimal bone density, it is advisable not to use GnRH agonists in these women.

Recommendations in the guideline:

Clinicians are recommended to use GnRH agonists (nafarelin, leuprolide, buserelin, goserelin or triptorelin), as one of the options for reducing endometriosis-associated pain, although evidence is limited regarding dosage or duration of treatment ***(based on level A evidence).***

Clinicians are recommended to prescribe hormonal add-back therapy to coincide with the start of GnRH agonist therapy, to prevent bone loss and hypoestrogenic symptoms during treatment. This is not known to reduce the effect of treatment on pain relief ***(based on level A evidence).***

The GDG recommends clinicians to give careful consideration to the use of GnRH agonists in young women and adolescents, since these women may not have reached maximum bone density ***(good practice point).***

Aromatase inhibitors

Aromatase inhibitors stop an enzyme (aromatase) that is needed in the production of estrogens in several cells of the body. The result is a very low **estrogen** level. These drugs have been used in other diseases, but they are only recently been used in endometriosis and not well studied yet.

Due to the side effects (vaginal dryness, hot flushes, diminished bone mineral density), aromatase inhibitors should only be prescribed to women in severe pain after trying all other options of medical and surgical treatment.

Aromatase inhibitors are not available in some European countries.

Recommendations in the guideline:
In women with pain from rectovaginal endometriosis refractory to other medical or surgical treatment, clinicians can consider prescribing aromatase inhibitors in combination with oral contraceptive pills, progestagens, or GnRH analogues, as they reduce endometriosis-associated pain. ***(based on level B evidence)***

What are the side effects of hormonal treatment?

Since the aim of treatment in endometriosis-associated pain is lowering the level of estrogens, the side effects are related to a low estrogen level. Besides that, the side effects are related to the drugs used to reach that low estrogen level.

Side effects are therefore related either to low estrogens (hormonal contraception, GnRH analogues) or to progesterone (hormonal contraception, progestagens).

Some examples of side effects of hormonal treatment for pain in endometriosis are headaches, acne, weight gain, vaginal spotting, fatigue and hot flushes.

These side effects differ strongly between treatments and between patients. As a result, a certain treatment can be a good option for one woman, but the same treatment can have severe side effects in another woman. **Your doctor should discuss side effects with you when prescribing hormonal treatment.**

Is surgical treatment an option for relieving pain symptoms?

Surgical treatment of endometriosis focuses on the elimination of peritoneal endometriosis/endometrioma/deep endometriosis and division of **adhesions**.

In the past, open surgery or laparotomy was used routinely. Nowadays, **laparoscopy** is used frequently and preferred since it usually results in less pain, shorter hospital stay, quicker recovery and a smaller scar. However, **laparotomy** and **laparoscopy** are equally effective in treating pain symptoms in women with endometriosis.

Therefore, clinicians should consider surgical treatment (elimination of endometriotic **lesions**) when they see endometriotic **lesions** during **laparoscopy** for diagnosis.

If deep endometriosis is suspected, doctors are recommended to refer their patient to a centre of expertise, as these surgeries may be difficult.

Recommendations in the guideline:

When endometriosis is identified at laparoscopy, clinicians are recommended to surgically treat endometriosis, as this is effective for reducing endometriosis-associated pain i.e. 'see and treat' ***(based on level A evidence).***

Clinicians can consider performing surgical removal of deep endometriosis, as it reduces endometriosis-associated pain and improves quality of life ***(based on level B evidence).***

The GDG recommends that clinicians refer women with suspected or diagnosed deep endometriosis to a centre of expertise that offers all available treatments in a multidisciplinary context. ***(Good practice point)***

Hysterectomy

If a woman has completed her family and other treatments do not work, removal of the ovaries with or without removal of the uterus (hysterectomy) can be considered. However, removal of the ovaries is a radical solution, since it results in so called surgical menopause with the side effects of menopause described above. It has to be mentioned that hysterectomy alone not always solves the problem, since most of the time endometriosis is left behind retroperitoneally and hence the pain symptoms remain present.

Recommendations in the guideline:
The GDG recommends that clinicians consider hysterectomy with removal of the ovaries and all visible endometriotic lesions, in women who have completed their family and failed to respond to more conservative treatments. Women should be informed that hysterectomy will not necessarily cure the symptoms or the disease. ***(Good practice point)***

Medical treatment before or after surgery

There is some controversy on this subject.

The guideline group does not recommend hormonal treatment before surgery to improve the results of the surgery. Of course, many women in pain get hormonal treatment during a waiting period before surgery. After surgery, starting with an oral contraceptive pill or using a levonorgestrel-intrauterine device may prevent recurrence of pain.

Recommendations in the guideline:
Clinicians should not prescribe preoperative hormonal treatment to improve the outcome of surgery for pain in women with endometriosis ***(based on level A evidence).***

After cystectomy for ovarian endometrioma in women not immediately seeking conception, clinicians are recommended to prescribe hormonal contraceptives for the secondary prevention of endometrioma ***(based on level A evidence).***

In women operated on for endometriosis, clinicians are recommended to prescribe postoperative use of a levonorgestrel-releasing intrauterine system (LNG-IUS) or a combined hormonal contraceptive for at least 18–24 months, as one of the options for the secondary prevention of endometriosis-associated dysmenorrhea, but not for non-menstrual pelvic pain or dyspareunia ***(based on level A evidence).***

Part 7: Endometriosis and infertility

Am I infertile because I have endometriosis?

Probably not, women diagnosed with endometriosis are not all infertile. In medical terms, **infertility** is defined as not reaching pregnancy after 1 year of regular intercourse. It is estimated that 60-70% of women with endometriosis are fertile and can get pregnant spontaneously and have children. Therefore, women not wanting to get pregnant should discuss their options for contraception with their doctor.

A proportion of women with endometriosis and **fertility problems** will stay involuntarily childless, but there are no exact data on how many. Of the women with **fertility problems**, a proportion will get pregnant, but only after medical assistance, either surgery or **medically assisted reproduction** (**IUI** or **IVF**). There is no evidence that hormonal treatment or alternative treatment enhances the chance of spontaneous pregnancy in women with endometriosis.

There is no best option for aiding infertile women with endometriosis to get pregnant. The decision on which option to take, surgery of medically assisted reproduction, should be based on type of disease, the doctor's preferences and the patient's preferences.

There is also no evidence that women with endometriosis have a higher risk of complications in pregnancy (birth defects, miscarriages), but please inform your doctor or midwife of a diagnosis of endometriosis.