

duce both estrogen and progesterone receptors. Gestrinone is the standard agent, which may be comparable to GnRH agonists in reducing pain and have fewer menopausal symptoms. Adverse effects of gestrinone include male hormone symptoms, such as acne, and possibly the development of unhealthy cholesterol levels.

RU486, or mifepristone, is another antiprogestin. In one six-month study, mifepristone improved symptoms and reduced endometrial implants without causing menopausal side effects. Unfortunately, it is commonly known as the "abortion pill" because its antiprogestin effects can induce miscarriage, and so its use is limited.



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HORMONAL TREATMENTS FOR ENDOMETRIOSIS



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HORMONAL TREATMENTS FOR ENDOMETRIOSIS

The basic approach in hormonal treatments for endometriosis is to block production of female hormones (estrogen and progesterone) or to prevent ovulation with other hormonal effects.

Inducing Pseudopregnancy: Agents that mimic a pregnant state block ovulation. The standard agents are oral contraceptives that contain estrogen and progestins. (Progestins are natural or synthetic forms of progesterone). Progestins may also be used alone, since they have specific effects that can cause the endometrial tissue itself to atrophy.

Inducing Pseudomenopause: Drugs that mimic menopause are those that reduce estrogen and progesterone to their lowest level. They include gonadotropin-releasing hormone (GnRH) agonists or gestrinone, an anti-progesterone.

Inducing On-going Blockage of Ovulation. Danazol, a derivative of male hormones, is a powerful ovulation blocker.

At this time, studies report that between 80% and 85% of women achieve pain relief after taking these agent. None of these agents appear to be any better than another in its ability to reduce pain. Women should discuss the side effects of particular medications with their physicians to determine the best choice.

It should be noted that these hormonal agents are used for pain relief only. None improve fertility rates and in some cases may delay conception.

Oral Contraceptives

Oral contraceptives combining estrogen and a progestin are most often used for treating endometriosis. When used throughout a menstrual cycle, they suppress the actions of other reproductive hor-

mones and prevents ovulation. There are many brands available. The estrogen compound used in most oral contraceptives is estradiol. Many different progestins are used, and there are many brands. None to date have proven to be superior over others. Women should discuss the best options for their individual situations with their physician.

Progestins

Progestins alone may be helpful and are the oldest drugs used for endometriosis. Progestins can prevent ovulation and reduce the risk for endometriosis in the following ways:

- Σ They reduce luteinizing hormone (LH), one of the reproductive hormones important in ovulation.
- Σ They change the lining of the uterus and eventually cause it to atrophy.
- Σ Some experts recommend them as the first choice for women with endometriosis who do not want to become pregnant. Progestins should not be given during the luteal phase (the premenstrual phase, which is 14 days before a period.)

Specific Progestins. Medroxyprogesterone (Depo-Provera), which is administered by injection typically every three months, are the standard progestins used. Others sometimes tried include norethisterone, dienogest, and lynestrenol. Some of these progestins may have fewer side effects than Depo-Provera. For example, in one study 94% of patients achieved some pain relief from norethindrone (Aygestin, Norlutate); only 7% dropped out because of side effects. A recent version of the intrauterine device (IUD) called the LNG-releasing intrauterine system (LNG IUS) releases progesterone and may have specific benefits against endometriosis.

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Side Effects of Progestins. Side effects of progestin occur in both the combination oral contraceptives and any contraceptive that only uses progestin, although they may be less or more severe depending on the form and dosage of the contraceptive. Side effects may include the following:

- Σ *Changes in uterine bleeding. Such as higher amounts during periods, spotting and bleeding between periods (called break-through bleeding), or absence of periods. Be sure to check with the physician if any of these occur.*
- Σ *Unexpected flow of breast milk. (Check with the physician if this occurs to be sure other abnormalities are not causing it.)*
- Σ *Abdominal pain or cramps.*
- Σ *Diarrhea.*
- Σ *Fatigue, unusual tiredness, weakness.*
- Σ *Hot flashes.*
- Σ *Decreased sex drive.*
- Σ *Nausea.*
- Σ *Trouble sleeping.*
- Σ *Acne or skin rash.*
- Σ *Depression, irritability, or other mood changes.*
- Σ *Swelling in the face, ankles, or feet.*
- Σ *Weight gain.*
- Σ *Progestins used in contraceptives that work only in the uterus, such as the LNG-IUS IUD, may not pose as high a risk for these side effects.*



GnRH Agonists

At this time, gonadotropin releasing hormone (GnRH) agonists are the most effective hormone treatments for endometriosis. They are able to block the release of the reproductive hormones LH and FSH. As a result, the ovaries stop ovulating and no longer produce estrogen. They relieve pain in most patients by the second or third month.



Specific GnRH Agonists. GnRH agonists include goserelin (Zoladex), busarelin, a monthly injection of leuprolide (depot Lupron), and a nasal spray, Nafarelin (Synarel). Studies have reported that nafarelin shrank all implants and significantly relieved symptoms in 85% of patients, delayed recurrence of endometriosis after surgery, and in comparison with leuprolide, was less expensive, had fewer side effects, and a provided better quality of life.

Common Side Effects. Commonly reported side effects (which can be severe in some women) include:

- Σ *Hot flashes and night sweats.*
- Σ *Reduced sexual drive.*
- Σ *Insomnia.*
- Σ *Headache.*
- Σ *Muscle aches.*
- Σ *Nausea and vomiting.*
- Σ *Memory loss.*
- Σ *Changes in the skin and hair.*
- Σ *Rapid heartbeat.*

- Σ *Vaginitis.*
- Σ *Dryness and/or burning sensations in the vaginal area.*
- Σ *Weight changes.*
- Σ *Depression. One study using the antidepressant sertraline (Zoloft) suggested that this agent and possibly other, similar agents known as serotonin reuptake inhibitors (SSRIs) may have specific actions that successfully treat depression from ovulation suppression.*

Side effects vary in intensity depending on the GnRH agonist. They may be more intense with leuprolide and persist after the drug has been stopped.

Risk for Osteoporosis. Estrogen loss from GnRH agonists increases the risk for bone loss and osteoporosis. Women ordinarily should not take them for more than six months. Certain other factors intensify the risk:

- ✦ *Smoking.*
- ✦ *A history of polycystic ovarian syndrome (with infrequent periods).*
- ✦ *Alcohol abuse.*
- ✦ *Long-term use of corticosteroids, which also reduce bone density.*
- ✦ *A family history of osteoporosis.*

Certain approaches may preserve enough estrogen to protect bones and still effectively relieve endometriosis symptoms.

- Σ *Add-back therapy provides doses of estrogen and progestin that are high enough to maintain bone density but are still sufficiently low so that pain-reducing effects of the GnRH agonist are preserved.*
- Σ *Taking GnRH agonists in very low doses is an alternate approach, but is still largely untested.*
- Σ *Adding a bone-protective agent called a bisphosphonate (alendronate or etidronate) may also be helpful.*

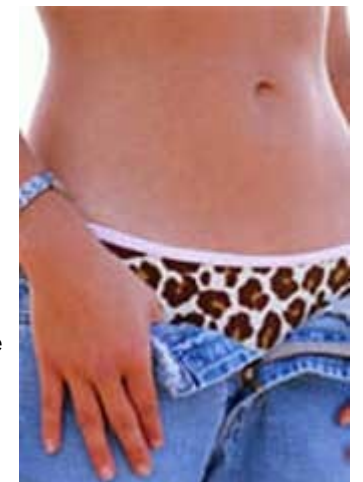
Other agents are being tested in combination with a GnRH agonist to preserve bone. They include parathyroid hormone or tibolone (available in Europe).

Tibolone is known as a selective estrogen-receptor modulator (SERM), which means it has some, but not all, of the effects of estrogen.

Effects on Pregnancy. GnRH treatments used alone do not prevent pregnancy. Furthermore, if a woman becomes pregnant during their use, there is some risk for birth defects. Women who are taking GnRH agonists should use non-hormonal birth control methods, such as the diaphragm, cervical cap, or condoms while on the treatments.

Danazol

Danazol (Danocrine) is a synthetic substance that resembles a male hormone. It suppresses the pathway leading to ovulation. Studies have shown symptomatic improvement in 90% of women. A high dropout rate occurs, most likely because of adverse side effects, particularly male characteristics, such as growth of facial hair, acne, weight gain, dandruff and deepening of the voice. Danazol may increase the risk for unhealthy cholesterol levels. A few cases of blood clots and strokes have also been reported, as well as rare cases of liver damage. One study reported that taking a low dose may relieve endometrial symptoms and reduce the risk for these side effects. Exercise may help reduce side effects. As with GnRH agents, pregnant women or those trying to become pregnant should not take this drug because it may cause birth defects.



Antiprogestins

Antiprogestins are promising agents for endometriosis because they re-