

Application of Dienogest In the Treatment of Endometriosis

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Abstract. Endometriosis is a condition that exists endometrioid epithelium and/or endometrialmatrix muscular layer, usually accompanied by inflammatory processes. The new progesterone, Dienogest (DNG), has no estrogen, anti-estrogen and androgen activities, at the same time, DNG has anti androgen activity. With a favorable safety and tolerability profile, DNG could relief pain and reduce ovarian endometriosis cysts, reduces the recurrence, meanwhile, DNG also has good effect on recurrent endometriosis. DNG mainly mediates the hypothalamus, pituitary and ovarian axis to inhibit the functions of ovarian. It can also inhibit the synthesis of estrogen metabolic enzymes, to reduce estrogen level. Through anti-inflammation and anti-angiogenesis, DNG could inhibit the development of pain, inhibit the occurrence and development of EMT lesions, which can be used as medicine for long-term management of endometriosis. Side effects such as uterine bleeding was observed, inform the patient in advance of compliance, careful long-term follow-up is required.

Keywords: Endometriosis, Dienogest, Pain, Cyst, Recurrence.

1. Introduction

Endometriosis (EMT) refers to the presence of endometrial tissue outside the uterine cavity and colonization and growth, mostly on the surface of the ovary and deep in the pelvic cavity. Clinical manifestations include dysmenorrhea, menstrual changes, pelvic caking, infertility and so on. The active cells of the endometrium that should be present in the endometrium can pass through the fallopian tube and enter the pelvic cavity, and affects 10 to 15 percent of women of childbearing age. An estimated 176 million women worldwide suffer from endometriosis-related pain; 20~50% of infertile women have endodynia and 71~87% of women with chronic pelvic pain. Severe dysmenorrhea, deep dyspareunia, difficulty defecating, chronic pelvic pain and reduced fertility are all major symptoms of endometriosis [1]. It is an estrogen-dependent disorder, also related to sex hormone, immunity, inflammation, heredity and other factors. The routine treatment of EMT is mainly surgery and drugs, but it's easy to relapse. However, some drugs have certain side effects, can not be used for a long time, surgical treatment is easy to relapse after operation.

Progesterone is used in treatment of EMT, since it can induce decidual-like changes in the endometrium, ultimately leading to atrophy of endometrial, and also, negatively inhibit the hypothalamic-pituitary-ovarian (HPO) axis [2]. The new progesterone, Dienogest (DNG), a favorable safety and tolerability profile, experiment showing that it could relief dysmenorrhea and reducing ovarian endometriosis cysts at the same time, and with the extension of medication time, the effect of reducing cysts is more significant [3]. DNG could be the alternative treatment of EMT. This paper is going to discussed the properties, and the application of DNG in treating endometriosis.

2. Characteristics of DNG

DNG is a kind of progestin that derived from 19-nortestosterone. It was also be born in two parental structures, the 19-nortestosterone and the progester-one derivatives. However, what DNG differ from the both is Dienogest could act as an antiandrogen, a typical progesterone derivative that

are associated with minimal changes in lipid and carbohydrate levels. DNG has high progesterone activity. Its oral semi effective dose is 0.11 mg/kg. Because it only binds specifically to progesterone receptor and has no estrogen, anti-estrogen and androgen activities, dinogestrin has ideal endocrine pharmacological properties. At the same time, DNG also has anti androgen activity. The reason may be that DNG has a same 18-carbon nucleus as estrane structure, but at the C-17, a cyanomethyl group take place of ethinyl group, and also add a double bond between C-9 and C-10 [4].

DNG has fewer effects on hepatic than other C-19 nortestosterone derivatives. DNG has a high affinity with progesterone receptor, as the PR, and rapidly and completely absorbed by oral administration. The metabolites could be eliminated rapidly from the urine within 24 h. DNG is easily get degraded by microorganisms. Within only 6.5-12h plasma half-life, there will no accumulation after a daily dosing since the plasma half-life is shorter than other progestins [5].

3. Application of DNG in endometriosis

3.1. Denorgestrel relieves the pain of endometriosis

Endometriosis patients are often accompanied by dysmenorrhea, dyspareunia, chronic pelvic pain and other pain symptoms, and about 30% of patients are accompanied by infertility [11]. About 85% of women experience dysmenorrhea during their menstrual cycle [6]. The main cause of dysmenorrhea may be uterine contractions caused by the release of prostaglandins [6]. The actual incidence of dysmenorrhea depends on complex and variable factors, making it difficult to assess [6]. So many women with dysmenorrhea who take painkillers don't think it's a symptom of endometriosis. Although this type of pain is very different from dysmenorrhea, it can also interfere with a woman's normal life that need to take analgesics regularly. Laparoscopy usually rules out pelvic inflammatory disease (PID) with intense congestion and pus flowing from the end of the pili of the tube, and cultures for chlamydia, anaerobe, and Gonorrhoeae should be performed [6]. Chronic PID will present as hydrosalpinx, usually with attachment adhesion. Extrapelvic endometriosis is found in almost every organ system and tissue in the body [6]. Many women who do not improve after laparoscopic surgery find no visible endometriosis at all on a second laparoscopy. The results showed that a large proportion of these women had irritable bowel syndrome. The pain of this condition is very similar to that of endometriosis, and there is evidence that these conditions coexist in many women.

Dienogest, as a new generation of synthetic progesterone, has a clear therapeutic effect in patients with EMT. It has good effects ease many like menstrual pelvic pain, dysmenorrhea as well as EMT associated pain symptom. DNG mainly mediates the hypothalamus, pituitary and ovarian axis to inhibit the functions of ovarian. It can also inhibit the synthesis of estrogen metabolic enzymes, to reduce estrogen level. Through anti-inflammation and anti-angiogenesis, DNG could inhibit the development of pain, inhibit the occurrence and development of EMT lesions [7]. It is also highly bound with PR, so it could resist the effects of estrogen. DNG is able to reduce the risk factors including CYP19A1, cyclo-oxygenase 2, prostaglandin E2, Inflammatory cytokines, nerve growth factor (NGF), Vascular endothelial growth factor (VEGF) that related with the pain that endometriosis brings or the growth of the disease [8]. Some study showed that, comparing with endometrial of females who without endometriosis, the rate of PR- β /PR- α in endometriosis patients is lower, and the ratio of estrogen receptor (ER)- β /ER- α is much higher. After treating with DNG, it improved the rate of PR- β /PR- α in endometriosis patients and decrease the ratio of ER- β /ER- α , showing that DNG could improve the progesterone resistance of endometriosis tissues, so that lead to the atrophy of endometriosis lesions [9].

A phase III, randomized, double-blind, placebo-controlled study in China included 255 patients aged 18-45 years from 23 centers who were diagnosed with endometriosis. 126 patients received DNG 2mg and 129 patients received placebo, the treatment time is 24 weeks. The results showed that during the treatment, the pain score improved from severe to mild or asymptomatic, and the DNG group was always higher than that of the placebo group [24].

Midkine(MK) protein is a nonglycosylated low molecule mass protein,also known as the Amphoterin 2.It could be involved in EMT disease mechanism by stimulate proliferation,migration, neuronal growth as well fibrinolysis.Compare with common situation,MK expression is much higher in EMT patients.By researchers,DNG could inhibit the MK level in EMT patients' abdomen [10].In addition,although patients in the DNG group had a higher EMT stage than other group that without DNG, the MK levels is quite lower,which may also indicate a direct effect of DNG on EMT.

3.2. DNG reduce the cyst of ovarian endometriosis

Ovary is the most likely site to be invaded by ectopic endometrium,with about 80% of lesions involving one side and 50% bilateral.

One study included 81 chocolate cyst of ovarian endometriosis patients who were treated with DNG and observed for 6 months shows that chronic pelvic pain and dyspareunia during intercourse were significantly improved,and ovarian cyst was also being significantly reduced[(52±22) mm³ vs. (32±12) mm³, P < 0.001] [11].This clinical experiment shows that, the DNG can effectively avoid the injury of ovary,and reducing the volume of ectopic lesion and treat pain.Some researchers conducted a retrospective study by using a conservative drug therapy instead of surgery, and the results showed that DNG could significantly reduce the lesions of ovarian endometrioid cyst, and there are no new lesions were generated during the treatment [12].

From the clinical trial produced by Lili. Duan,94 EMT patients was randomly divided into two groups. First set group were taken conventional medicine from the first day of menstruation, and continue a 6-period of menstruation long treatment. The other set group taking both conventional medicine and dienogest, and continue a 6-period of menstruation long treatment. The result of treatment showed there are totally 38 patients in the second set group have significantly decreasing of pelvic lump, with approximately 80.8%. Comparing with the group without DNG participated, there are only 32 patents shows a noteworthy decrease, with 68.0%. From this trail, the DNG have a remarkable effect on decreasing the size of pelvic lump [13].

DNG directly inhibited the proliferation of endometriosis stromal cells accompanied by G0 / G1 phase cell cycle arrest [14]. At the same time, DNG could also induce the synthesis of P21 gene by up-regulation of core proteoglycan. In this case, it could induce cell cycle arrest [15]. All showed the anti-proliferation effect of DNG on endometriosis stromal cells.

3.3. DNG reduces recurrence of endometriosis

EMT is also mainly treated by laparoscopic surgery.Ovarian endometrioid caused by periodic bleeding in the deep part of ovary is the most common type of EMT.When the diameter of ovarian endometrioid cyst is >4cm,surgical treatment is recommended.There is a very clear advantage of laparoscopic surgery that can adequate exposure,magnification the minimal tissue Handlin,strict attention to Haemostasi,prevention of tissue desiccation,exposie the site of the operation and giving the doctor a good view.These advantages of laparoscopic surgery mean that patients can return to daily activities more quickly.But laparoscopic surgery still has major drawbacks,which is esay to recur.Recurrent EMT includes symptom recurrence (subjective symptoms) and disease recurrence (objective manifestations).Repeated surgery after recurrent endometriosis can cause severe ovarian damage. It can lead to infertility.In addition to chronic inflammatory adhesions associated with endometriosis,surgery for recurrent endometriosis becomes more challenging due to the development of postoperative adhesions.Therefore,the surgical treatment of recurrent endometriosis should be carefully considered [16].The patients with recurrent endometriosis underwent repeat surgery was 30.7%.The prevention of recurrence focuses on the initial treatment.

DNG may be an alternative treatment to avoid repeated surgery in the early stage of endometrial tumor recurrence.Patients who received postoperative DNG reported a cumulative recurrence rate of 4% five years after surgery,significantly lower than patients who did not receive any postoperative medication.

Ozaki et al divided 70 patients with endometrioid cysts of ovary who planned laparoscopic surgery into two groups and gave DNG 2mg / D and low-dose sustained-release goserelin acetate 1.8mg/month respectively. The results showed that the pain digital score and Kupperman score of the two groups decreased after 4 months of preoperative drug treatment, and the DNG group was lower than the goserelin group, indicating that the preoperative application of DNG can alleviate the symptoms. If the postoperative patients have no fertility requirements, DNG can be used to delay the recurrence [17]. In another research Sugimoto et al found that in the treatment of DNG, the average maximum diameter of ovarian endometrioid could be reduced to 30% of the initial size at 15 months, but the size increased slightly at 18 months (49.6% of the initial size). They believed that this was related to the short-term discontinuation of DNG. After the resumption of treatment, the capsule diameter was further reduced (27.1% of the initial diameter at 24 months), and the level of serum marker carbohydrate antigen (CA) 125 decreased steadily, it is suggested that DNG may need to be used for a long term [18].

Ikoshiba gave DNG to 7 patients with recurrent EMT. After 24 months of treatment, the recurrent EMT disease of 4 patients completely disappeared. Lee also confirmed the efficacy of DNG on recurrent EMT. They evaluated the changes of EMT related pain score, CA125 and disease size of 121 patients with recurrent EMT before and after DNG use. It was found that the pain score and CA125 value of patients decreased and the symptoms decreased after treatment, indicating that DNG performed well both in subjective symptom level and objective performance [19].

3.4. DNG for deep infiltrating endometriosis

Deep infiltrating endometriosis (DIE) can invade all organs in the front, middle and rear parts of the pelvic cavity. DIE can cause dysmenorrhea, chronic pelvic pain, sexual intercourse pain and so on. Due to the ectopic disease is located in the deep pelvic cavity, it is often complicated with extensive pelvic adhesion, insensitive to drug treatment and high degree of operation.

Studies have shown that DNG is effective in the pain management of DIE. Leonardo Pinto et al [20] enrolled 30 patients with DIE complicated with dysmenorrhea, chronic pelvic pain and sexual intercourse pain into the study and treated them with DNG 2mg/d for a total of 12 months. The results showed that various pain scores decreased, the number of days of severe pain per month decreased, and the score of quality of life increased, but the nodule size of DIE did not decrease. In a study on the compliance of 59 patients with DIE after resection, DNG 2mg / d continuous striation treatment was given for 31 months. The results showed that there were 3 patients with recurrence according to imaging examination, and no pain recurrence was observed [21]. It is suggested that DNG can effectively prevent DIE recurrence and is of great significance for long-term drug of DIE management.

3.5. DNG bleeding patterns

As with other progesterone, changes in bleeding patterns are common in the early days of denorgestrel use. There is no need to worry too much about this situation clinically. Over time, the bleeding symptoms will gradually disappear. Therefore, before using denorgestrel, it is necessary to communicate the bleeding problem with patients in advance to avoid affecting compliance [22].

4. Conclusions

Endometriosis is a chronic disease with no cure and requires long-term management. DNG is effective in alleviating pain in endometriosis, reducing cyst volume and decreasing the probability of recurrence after surgery. Hormone therapy with DNG immediately after recurrence of endometriosis is also a viable treatment option that reduces the need for repeated surgery. It may also help protect ovarian reserve and maintain fertility in patients with endometriosis. Further large-scale prospective studies are needed to clarify our findings.

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