Review Article

iMedPub Journals
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Journal of Medical Research and Health Education

2017
Vol.1 No.3:11

Progestins in the Medical Management of Endometriosis

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Received date: September 12, 2017; **Accepted date:** October 24, 2017; **Published date:** October 30, 2017

Citation: Singh P, Batra S. Progestins in the Medical Management of Endometriosis. J Med Res Health Educ 2017, Vol. 1 No. 3: 11.

Abstract

Endometriosis is a chronic and debilitating disease affecting a large number of women. It is one of the important etiology of chronic pelvic pain and dysmenorrhea. Prevalence is more in women with infertility. It poses a major challenge for clinicians as there is no permanent cure and even after definitive management, there are high chances of recurrence.

The classical triad of dysmenorrhea, dyspareunia and infertility as an important diagnostic feature present in these women. As it affects all the aspects of life of affected woman, a lot of research is directed to find out ideal medication for endometriosis, which has good efficacy, is tolerable, cost-effective, easily available, which targets the basic pathology of disease and cures it. However, such cure is yet to be found. Very similar to ideal agent is a new novel molecule, Dienogest. Its profile is discussed here along with the various studies showing its efficacy and pharmacology and comparison with other progestins already being used since long. Other potential progestins are also discussed providing a whole spectrum of drugs with different efficacy and profiles.

Keywords: Dienogest; Endometriosis; Levo-norgestral intrauterine system; Medroxy progesterone acetate; Dysmenorrhoea; GnRH; DMPA

Introduction

Endometriosis is characterized by the presence of endometrium-like tissue outside the uterus, which then induces a chronic, inflammatory reaction [1]. It is a chronic and debilitating illness which affects the women's menstrual cycle and has profound impact on her social and psychological life, altering her work- life balance. The exact prevalence of endometriosis is unknown but estimates range from 2 to 10% of women of reproductive age, to 50% of infertile women [2,3]. In the absence of treatment, endometriosis is usually a chronic and progressive condition [4]. Management of endometriosis has been changing over period of time, shifting focus from radical surgery to more conservative approach. Researches are ongoing for finding more effective agents, which have high tolerability and safety profiles.

Many guidelines favour use of steroids in endometriosis [5-8]. Oral progestogens and combined oral contraceptives effectively relieve pain of dysmenorrhea as well as take care of heavy menstrual bleeding, and are usually well tolerated. Danazol which was once a preferred drug is no more a initial choice now due to its androgenic side effects profile. Progesterone and Combines OCPs are preferable to gonadotrophin releasing hormone agonists and aromatase inhibitors [9] as a first line therapy. Recent trend towards use levonorgestrel intrauterine system, has evidence of safety, tolerability and efficacy [10,11]. Subdermal etonogestrel implant, though efficacious in initial reports, mostly case reports; has yet to prove its long term efficacy and benefits over the existing treatment.

Oral contraceptives and synthetic progestins have proven their value in endometriosis over a period of time, especially in women not desiring fertility. Though evidence is limited for effectiveness, hormonal contraceptives are widely used as treatment for dysmenorrhea and pelvic pain in women with endometriosis, which could be due to some practical advantages, including contraception, long-term safety and control of menstrual cycle [12]. There are certain limiting factors which include long-term administration, risk of thromboembolism, high rates of recurrence after discontinuation, and impaired fertility due to contraceptive action.

Many recent studies have documented and compared the efficacy, types and routes of different synthetic progesterones in management of endometriosis that is chronic pelvic pain, dysmenorrhoea, dyspareunia and infertility. The current ongoing trials have favored the use of progestins in primary and post-operative management of endometriosis. These shifting trends towards conservative management of endometriosis are due to introduction of progestins with high efficacy and lesser side effects as compared to traditional oral contraceptives and older progestins. Also, because the various studies suggest almost similar effect of progestins in dysmenorrhoea and chronic pelvic pain as primary surgery or GnRH.

In this article we will discuss progestins, with special emphasis to Dienogest in the medical management of endometriosis.

Mechanism of Action

Progesterone addresses basic pathology of endometriosis, that is induces decidualization of the endometrium, inhibits estrogen-induced mitosis, alters estrogen receptors, inhibits angiogenesis, inhibits expression of matrix metalloproteinase (MMP) needed for the growth of the endometriotic implants [13,14].

The main progestins which have been in active use in the past 5 years are Dienogest and levonorgestrel Intrauterine device. Other progestins include medroxyprogesterone acetate in depot form, etonogestrel implants, norethisterone acetate in oral form and combination of Dienogest and estradiol valerate. Oral norethindrone acetate and subcutaneous DMPA have long been approved by the U.S. Food and Drug Administration (FDA) for treatment of endometriosis associated pain, but a higher dose is needed as compared to other indications.

In this article, we will discuss and compare the use of progestins specially, Dienogest in the primary and post-operative management of endometriosis in women not desirous of conception.

Dienogest: A Newer Progesterone

Dienogest is 19-nortestosterone derivative, it has the pharmacological properties of 19- nortestosterone as well as natural progesterone derivatives [15]. It differs from other 19-norprogestins by possessing a cyanomethyl group instead of an ethinyl group in the 17a-position [16]. It shows a high selectivity for the progesteron receptors and a strong progestogenic effect on the endometrium. It has the beneficial antiandrogenic properties, similar to other progesterone and causes minimal changes in lipid and carbohydrate metabolism [17]. Dienogest exhibits a low binding affinity to the androgen receptor and a negligible affinity for estrogen, glucocorticoid and mineralocorticoid receptors [18,19].

Oral administration of Dienogest almost completely gets absorbed and has high bioavailability (~91%). The T 1/2 of Dienogest is relatively short (~10 h), so it does not gets accumulated after repeated dosing [14]. Maximum serum concentrations are reached within approximately 2 hours of administration [20].

Dienogest as like other Progestogens, are metabolized mainly by the cytochrome P450 3A4 (CYP3A4) system.

It creates an endocrinal environment which is hypoestrogenic and hyperprogestogenic, which causes the decidualization of ectopic endometrial tissue after immediate adminstration. Prolonged treatments, results in atrophy of the lesions. It inhibits, growth of ovarian follicles therby causing the decrease of estradiol levels [13]. Dienogest has anti-inflammatory activity through modification of proinflammatory markers, which has been demonstrated in various *in vitro* and *in vivo* clinical experiments [20].

Two independent trials in two different continents Europe and Asia (Japan) have systemically investigated this drug for the treatment of endometriosis; drug dosage range were also compared. These were long-term studies [21,22].

Dienogest mechanism of action

It suppresses ovulation by inhibition of hormonal stimulation, which then causes inhibition of endometrial cell proliferation, increases apoptosis in eutopic endometrium and induces decidualisation. This if followed by atrophy of atrophy of ectopic implant. It also reduces menstrual blood flow and hence decreases tubal reflux of menstrual endometrium [23-25].

Dienogest has showed good efficacy for treatment of endometriosis whether it was compared against placebo or other drugs.

Dienogest versus placebo

Strovitzki compared Dienogest initially against placebo [26] in females undergoing laproscopy, for 12 weeks. There was a significant decrease in analgesic intake in women who were on Dienogest as compared to other group, though decrease was observed in both groups. Also reduction in VAS score, bladder and bowel symptoms and improvement in quality of life was noted in Dienogest group.

Dienogest v/s GnRH agonist

Strovitzki [27] compared Dienogest against Leuprolide acetate, the long acting GnRH analogue in endometriosis management. The primary variable studied was change in pain of endometriosis. The primary efficacy variable was the absolute change in endometriosis-associated pelvic pain from baseline to the end of treatment which was 12 weeks, Though both the drugs were associated with significant decrease in VAS score (reduction in Dienogest group was 47.5 (+28.8), and 46.0 (+24.8) in Leuprolide Acetate group. He also assessed Biberoglu and Behrman (B and B) severity profile, (for pelvic pain, dysmenorrhoea and dyspareunia) and physical findings (pelvic tenderness and induration) [28] and Quality of life using the Short Form-36TM (SF-36) Health Survey [29]. Dienogest performed slightly better or was comparable in most of these aspects.

The comparable efficacy of Dienogest to LA was demonstrated as the severity of the symptoms of pelvic pain, dysmenorrhea and dyspareunia and signs of pelvic tenderness and induration reduced in both the groups without significant difference. Women in both the groups reported headache and was the commonest complain. Women receiving leuprolide faced more of hot flushes which is explained by hypo-oestrogenic state caused by GnRH agonists. Estrogen levels remained stable in women receiving Dienogest, also there was not much alteration in lipid profile. Serum bone-specific alkaline phosphatase levels increased, which indicate bone

resorption decreased in Dienogest and increased in LA group. Mean lumbar BMD decreased in women treated with leuprolide at 24 weeks whereas it increased in women who took Dienogest, which was clinically significant.

Infrequent bleeding was noted in LA group whereas prolonged bleeding was a common finding in Dienogest group, however after some time, amenorrhoea was noted in both the groups. There was no weight gain and rise in blood pressure in Dienogest group; however a woman developed severe depression in Dienogest group.

Another study from the same author [30] analysed the secondary efficacy and safety outcomes of Dienogest in women with endometriosis. Approximately half women of their study group were free of pain, remaining also had some pain relief. Dysmenorrhea and dyspareunia significantly improved. The effects were evident from 4 weeks that is the first follow up.

1% women in Dienogest and 2% in LA group still had significant symptoms. Women seem more satisfied with Dienogest than Leuprolide Acetate group, in their ability perform daily work and had higher energy levels, and social activities; all this indicated that quality of life was better with Dienogest. Another study [31] comments on the impact on daily life of women with endometriosis, as there is increased chances of absenteeism from work, work impairment and impairment in daily activities.

Harada et al. [32,33] compared Dienogest with buserelin (intranasal) and triptorelin in endometriotic women. Outcomes with other studies also demonstrate Dienogest at par with these GnRH agonists in controlling most of the clinical symptomatology of endometriosis.

Dienogest seems to have some advantages over GnRH, in certain aspects of QoL, safety, and tolerability, which may be especially advantageous when planning long-term treatment.

Dosing

Dienogest in daily doses of 1,2 and 4 mg for 24 weeks were given in a Japanese study. Equal efficacy and safety was seen with 2 and 4 mg doses [33]. Higher reductions in estradiol levels were associated with the 4 mg dose. It was suggested that 2 mg daily may offer least potential for adverse effects on bone mineral density as compared to 4 mg.

Kohler [34] also compared 3 doses of Dienogest in patients with endometriosis that is 1, 2 and 4 mg over a period of 24 weeks. At 2 and 4 mg, there were similar responses and tolerance but more prevalence of irregular PV bleeding in 4 mg group, which improved over period of time. Study in 1 mg group was stopped prematurely because of unsatisfactory bleeding pre vaginum patterns.

Dienogest in higher doses

A pilot study [35,36] was carried out on 21 women suffering from endometriosis. Dienogest was given at 20 mg/ day. There was almost negligible impact of high-dose Dienogest on haemostasis, thyroid and adrenal function, glucose and lipid metabolism, liver function, electrolyte balance and haematology establishing safety of this drug at higher doses.

Though slight increase in prothrombin fragment 1+2, antithrombin III and protein C were noted which were at normal range at 24 weeks. HDL-3 Cholesterol at 24 weeks increased beyond the reference values. This is in contrast to Medroxy Progesterone Acetate (MPA) which significantly increases LDL and triglyceride levels [37,38], decreases HDL [38,39] increase total and free cholesterol [39-41], reduce levels of apolipoprotein A1 [42]. MPA also reduced glucose tolerance and increased insulin resistance [43,44].

Danazol reduces HDL cholesterol, increases LDL cholesterol and increases triglycerides levels [40], apolipoprotein A and B.

Dienogest- long term administration

Petralgia [45] as part of pilot project gave Dienogest 2 mg/day for 53 weeks in women who completed 12 weeks of treatment. These women were evaluated in a 24-week follow-up after treatment discontinuation.

Progressive decline in VAS score was noticed with no/ minimal changes in laboratory parameters and body weight. Decrease in endometriosis associated pelvic pain persisted even for 24 weeks after stopping treatment. This observation of prolonged pain relief even after the return of normal menses suggests a sustained long lasting effect on endometrial lesions. One plausible explanation for effect could be reduction in endometriotic lesions during Dienogest treatment [46]. Irregular uterine bleeding is a known common adverse effect of all long-term progestin treatments [47], if patient is counseled, better acceptability may be expected.

Therefore, Dienogest may represent an effective long-term treatment option for women with endometriosis.

Strovitzki et al. [27] reported efficacy in pain variables and no significant changes in clinical parameters were observed. Similar results were obtained when Dienogest was compared with buserelin over 24 weeks [31].

Dienogest and ovulation

Dienogest at 2 mg/day inhibits ovulation [48,49]. Klipping [48] compared different doses of Dienogest (0.5, 1, 2, or 3 mg/ day), for effect on ovulation. They observed that ovulation occurred in few women receiving 0.5 and 1 mg Dienogest but no ovulation was seen in 2 and 3 mg of this drug group. Ovarian activity (follicle size>13 mm, serum E2 levels>27 pg/ml, low progesterone) was recorded in more than half of women receiving 0.5 and 1 mg DNG, but in less than one third women of the 2 and 3 mg DNG groups. Estradiol levels decreased in women receiving Dienogest 2 mg but not much. Hence, they concluded that a dose of 2 mg Dienogest daily inhibits ovulation, but suppres estrogen production only moderately.

Dienogest plus estrogen

A recent study [50] retrospectively compared the impact of post-operative estradiol valerate+Dienogest (Group A) and levonorgestrel-releasing uterine device (Group B) in women undergoing surgery for peritoneal endometriosis, ovarian endometrioma, or excision of rectovaginal septum nodules.

They reported difference in VAS score; recurrence of endometriosis and treatment satisfaction. At 12 month, there was a significant decrease in VAS score and CA-125 levels ($P<0.05$). Relapse rate in group A was slightly lower than group B but was not significant ($P=0.41$). Similar findings were noted at 24 months. Treatment satisfaction was more in group B (levonorgestral intra uterine system). Treatment satisfaction was defined by the percentage of women who completed their treatment successfully. Such difference in treatment satisfaction can be explained by one time application of LNG-IUS and comparatively lower cumulative cost.

Results of a Multicentre RCT [51] were published in 2015 which compared combination of Estradiol valerate and Dienogest for 9 months with GnRH analogue given for 6 months post operatively. Both drugs were found to be equally effective but Dienogest was better in terms of tolerability and side effects profile. With GnRH analogues, significant difference in vasomotor symptoms, decreased libido and discomfort due to amenorrhea, undesired effects on bone mineral density and climacteric symptoms were observed.

As a very common side effect noted with Dienogest is irregular PV bleeding, a study [52] in Italy was conducted using quadriphasic Dienogest and estradiol valerate given cyclically and NSAIDS. Improvement in pain and quality of life was noted in Dienogest group but not in NSAIDS group. Quadriphasic estrogen valerate, had decreasing amounts of E2 led to better cycle control.

Dienogest and anatomical changes

A retrospective study was conducted in Japan [53] in women with diagnosed (both radiologically and surgically) endometriosis, adenomyosis or chocolate cyst, with the aim to find adverse effects and patient satisfaction in women receiving Dienogest over a period of 53–120 weeks. There was marked reduction in size of chocolate cyst. Thickness of myometrium also decreased in cases of adenomyosis. These effects were short term, and increase in size of chocolate cyst and myometrial thickness was observed on leaving treatment, however on re-starting treatment, they further reduced.

At dose of 2 mg/day, E2 levels reduced in cases (<60 pg/mL) but in some patients levels were reaching 120 pg/mL and follicular growth without ovulation was observed. In such patient higher doses of Dienogest will be useful, especially in patients with decreased ovarian reserve. This implies that in women with endometriosis, in order to prevent ovulation and hence preserve ovarian reserve, higher doses of Dienogest may need to be given.

Dienogest versus norethisterone

Norethindrone acetate is approved by the U.S. Food and Drug Administration and the Italian Ministry of Health for the treatment of endometriosis.

Vercellini [54] compared the long used drug Norethindrone acetate 2.5 mg/day with Dienogest 2 mg/day. Alteration in pain symptamatology, sexual function, psychological status, quality of life related to health. They reported marked improvement in anxiety and depression and the Female Sexual Function Index (FSFI) score in both the groups without much difference between the two groups. Dienogest had better tolerability, but pain and abnormal bleeding profile, health-related quality of life or sexual functioning was same in both the groups. Net en had better effect on psychological profile and better scoring on depression scale compared to Dienogest. This may be due to androgenic effect of net en which is lacking in Dienogest [55,56].

14% in net en group and 9% in Dienogest group reported decreased libido; and weight gain was more common in net en group. Dienogest is costlier than net en which was one of the major reasons for some women in Dienogest group to discontinue it.

Improvement in quality of life

Many studies report improvement in quality of life when measured by SF 36 scores with regard to physical function, physical role, body pain, general health, social function and emotional role categories [52,57,58]. Sexual improvement in terms of female sexual dysfunction (FSD) and self-administered Female Sexual Function Index (FSFI) and on Female Sexual Distress Scale (FSDS) in women taking Dienogest for endometriosis [52,58].

Pregnancy has also been reported while on Dienogest treatment [22]. Dienogest was stopped and pregnancy resulted in a live and healthy baby.

Dienogest, although near to being the ideal candidate for medical management of endometriosis is not free of side effects. The most frequently reported adverse effects are irregular PV bleeding, headache, acne, nausea, weight gain, breast tenderness, depressed mood and flatulence [27,47,52,55,56]. The cause of atypical genital bleeding was thought to be due to breakthrough of pseudodecidualized endometrium [59]. One study report [32] development of peritonitis in woman taking Dienogest which improved after stopping treatment.

As there are cases of severe depression with Dienogest, patients with pre- existing depression demand careful monitoring. Contraindications include active venous thromboembolic disease, past or present cardiovascular disease, diabetes with cardiovascular involvement, current or past severe hepatic disease/tumours, hormone-dependent malignancy and undiagnosed vaginal bleeding.

There is moderate suppression of estrogen levels after taking Dienogest. The Estrogen threshold hypothesis which

proposes that the optimal therapy of endometriosis should provide suppression of estrogen levels sufficient to inhibit endometrial stimulation but moderate enough to prevent hypoestrogenic adverse effects such as BMD loss [60].

The use of the levonorgestrel-releasing intrauterine system for treatment of endometriosis after surgery was first reported by Vercellini et al. in 1999 [61]. Levonorgestrel-releasing intrauterine device contains 52 mg of Levonorgestrel and releases approximately 20 mcg every day over a span of 5 years. The levonorgestrel intrauterine system is not approved by the FDA for treatment of endometriosis-associated pain. Because of its local action, its systemic effects are less; hence less progesterone induced side effects and better patient tolerability. Use of levonorgestrel-releasing intrauterine system has been shown to be effective in endometriosis, especially in rectovaginal disease [62,63], but there is evidence of removal of LNG IUS because of unacceptable irregular bleeding, persistent pain, or weight gain [63].

A double-blind randomized controlled trial [64] was conducted in 55 patients with endometriosis undergoing laparoscopic conservative surgery; patients were randomized to levonorgestrel-releasing intrauterine system or expectant management group. Both groups showed improvement with respect to Dysmenorrhoea and chronic pelvic pain improved in both groups but in LNG IUS group dyspareunia also improved. Improvement in quality of life was also noted in LNG IUS group.

LNG- IUD v/s DMPA

Wong et al. [65] compared LNG IUS with DMPA in terms of efficacy, prevention of lesion recurrence and patients' tolerance over a period of 3 years. There was improvement in both the groups but with not much difference, however bone loss was observed in DMPA group which was not seen in LNG IUS group. Pain score was significantly improved, but dyspareunia, bowel-bladder symptoms did not improved much.

LNG- IUD v/s GnRH agonists

LNG IUS has also been compared to GnRH agonist with similar results in pain scores and quality of life in both groups, with predominant amenorrhea and postmenopausal symptoms in GnRH groups and irregular PV bleeding in LNG IUS group [66,67].

Etonogestrel

Etonogestrel impant has been used as contraceptive. It is Inserted intradermally in the arm, it offers contraceptive benefits for 3 years. It is commonly marketed as Implanon and Nexplanon. Reported rates of improvement in dysmenorrhea in women using it for birth control prompted research for its use in endometriosis [68].

A RCT [69] compared the therapeutic efficacies of depot medroxyprogesterone acetate injection and Implanon with regard to pain relief, change in VAS score and bleeding pattern and satisfaction over a period of 1 year. Improvement in VAS score noted in both groups, more in implanon, but without significant difference ($p<0.36$). Percentage usage of analgesics also decreased. High satisfaction was noted in both groups. Like other studies evaluating progesterone, most effect was noticed in 3 month and not much change in VAS score after 6 months.

Acne, loss of hair, weight gain, breast tenderness and prolonged PV bleeding were side effects commonly observed in both treatment groups. 2 patients (10%) in DMPA group had severe depression after treatment. Withdrawal from study was more in DMPA group because of various reasons.

Although DMPA therapy is effective in reducing endometriosis-associated pelvic pain, it is often accompanied by some weight gain, decreased libido, acne and reversible bone loss. This may adversely affect a woman's quality of life and preclude long-term use [70,71].

Weight gain is possibly due to the negative influence on lipid metabolism [72].

Another study mentions the impact on metabolism during Implanon and DMPA use. Implanon was found to have only a slight impact on carbohydrate metabolism [73]. DMPA influenced glucose–insulin metabolism adversely [43,44,74]. Also it increases LDL, triglyceride and cholesterol levels and decreases HDL and apolipoprotein A1.

In contrast to DMPA, Implanon does not reduce the bone mineral density and hence can be used in young women who have still not achieved their peak bone mass [75].

Cyproterone Acetate

Cyproterone acetate is a synthetic oral progestin with anti-androgenic properties due to competitive inhibition on cytoplasmic testosterone receptor. It also has a negative feedback effect on H-P-O axis. It is mainly used in patients with hirsutism. Although CPA is widely used off-label for the treatment of symptomatic endometriosis, the literature supporting the use in this indication is limited.

Vercellini [76] compared low-dose cyproterone acetate with oral contraceptive for treatment of recurrent pelvic pain after surgery for endometriosis. The scales for evaluating pain, health-related quality-of life, psycho-emotional status, and sexual functioning were chosen for reliability, simplicity, and acceptability [77-81]. Although the differences in various health-related quality-of-life score between the two study groups were limited, patients in the cyproterone acetate group reported slightly better health. Both were similarly effective in Reduction in recurrent pelvic pain after endometriosis surgery was less in cyproterone acetate group. Size of previous endometriomas was same, no new endometriotic cysts developed. There was not much change in lipid profile. Hence, cyproterone acetate may be preferable when estrogen-related metabolic and subjective side effects are considered particularly undesirable.

Conclusion

As endometriosis is a chronic progressive condition, it demands thorough evaluation of the need of patient and case selective decision. Because endometriosis is associated with infertility and most of the drugs used act as contraceptive, surgery does form an important element in management of endometriosis. There are high chances of recurrence in patients even after surgical management. So, any corrective surgery should be followed by appropriate agents to minimize chances of recurrence and decrease morbidity. In patients not desiring fertility, medical management is an essential key to decrease the disease burden, both as primary management and post-operative and to benefit lives of millions of suffering women.

Progestins are definitely cost effective options and hold a promising future for patients with endometriosis. Studies have compared Dienogest to GnRH agonists [26-32] Depot MPA, NET –EN and oral contraceptives. However, very limited studies are available comparing Dienogest to LNG- IUS: another promising tool in managing endometriosis. Dienogest is safe, efficient, cost effective, has high patient acceptance, no androgenic or anti- estrogenic side effects. Hence, should be accepted for primary as well as post-operative management in patients of endometriosis. However, as endometriosis is a lifelong condition, there are concerns about prolonged treatment with Dienogest. There is also need to ensure safety profile of Dienogest in prolonged treatments. On the other hand, as there is advantage of avoidance of daily oral dosing in LNG IUS and etonogestrel implants, as well as no significant biochemical changes in studies done till now, they hold promise in long term management of endometriosis without compromising compliance. There is need of high quality studies comparing these new progestins in long term management of endometriosis.

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