Review Article

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Endometriosis–what is New in Medical Management with Progesterones

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Abstract

Endometriosis affects women in their reproductive life and is a chronic disease. It is an important causes of dysmenorrhea, chronic pelvic pain and infertility. Diagnostic and therapeutic challenge is faced by clinicians as the disease tends to come back. Management is usually directed at relieving the symptoms and improving the chances of fertility which is either medical or surgical or a combination of the two. Some women with endometriosis might be asymptomatic, most have chronic abdominal &/or pelvic pain. Research is directed to find out ideal medication for endometriosis, with good efficacy, minimal or least side effects, cost- effective, and cantargets the basic pathology of disease to cures it. However, such cure is yet to be found.

Many drugs are used to treat endometriosis- NSAIDs, combined oral contraceptive agents, Progesterones (oral, injections and local as intra uterine device. Every drug has its side effects and safety profile. Progesterones are generally preferred in very young as well as older women who cannot take long term OCP due to estrogenic side effects or contraindication

Dienogest, a newer progestogen is closer to the ideal agent. Its profile is discussed below along with comparison with other progestins which are already being used. Other potential progestins are also discussed providing a whole spectrum of drugs with different efficacy and profiles.

Keywords: Endometriosis; Progesterones; DMPA; Dienogest; Levonorgestral Intrauterine System.

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Introduction

Presence of endometrial-like tissue outside the uterus, like ovary, tube, pelvic or abdominal peritoneum or even at distant sites is endometriosis. This ectopic endometrium induces a chronic, inflammatory reaction [1]. It is a chronic & debilitating illness which affects the women's menstrual cycle, reproductive potential and has profound impact on her social and psychological health, altering her work- life balance. The exact prevalence of endometriosis is unknown but estimates range from 2 to 10% of women of reproductive age, and as high as 50% in infertile women [2,3]. In the absence of treatment, endometriosis is usually a chronic and progressive condition.

Management of endometriosis has been changing over time, shifting focus from radical surgery to more conservative approach. Both oral progestogens and combined oral contraceptives are effective in relieving pain. They are generally well tolerated and are initially preferable to Danazol, Gonadotrophin releasing hormone agonists and Aromatase inhibitors [5]. There is trend towards use of the delivery systems like the Subdermal Etonogestrel implant & the Levonorgestrel intrauterine system [6].

Oral contraceptives and synthetic progestins have proven their value in endometriosis over a period of time, especially in women not desiring fertility.

Hormonal contraceptives are widely used as treatment for pain in women with endometriosis, which might be due to added advantages, including contraception, safety profile over the years and control of menstrual cycle [7]. Long-term administration in women over 35years, risk of thromboembolism, high rates of recurrence after discontinuation, and impaired fertility due to contraceptive action are some of the disadvantage of OCPs.

Recent trends for use of progestins in primary and post- operative management of endometriosis is promising. Newerprogestinshave high efficacy and lesser side effects as compared to traditional oral contraceptives and older progestins. Also, various studies have suggested almost similar effect of progestins in dysmenorrhoea and chronic pelvic pain as primary surgery or GnRH.

Progesteronesinduces decidualization of the endometrium, inhibits estrogen-induced mitosis, alters estrogen receptors, inhibits angiogenesis and expression of matrix metalloproteinase (MMP) needed for the growth of the endometriotic implants.

The main progestins which have been in active use in the past 5 years are Dienogest & Levonorgestrel Intrauterine device. Other older progesterones – Medroxy progesterone acetate, Norethisterone Acetate, Inj DMPA also used. Etonogestrel implants and combination of dienogest and estradiol valerate is also showing promise; but not all of these are approved by USFDA for this purpose.

Here we discuss and compare the use of oral progestins - Dienogest in the primary and post operative management of endometriosis in women not desirous of concepion.

Dienogest

Dienogest is a derivative of19-nortestosterone, differing from other 19 norprogesterones by having a cyanomethyl group instead of an ethinyl group in 17a-position [8]. It has high selectivity for the progesteron receptors and a powerful progestinic effect on endometrium. Its antiandrogenic properties, causes minimal changes in serum lipid profile and carbohydrates metabolism [9]. Dienogest exhibits a low bindingaffinity to the androgen receptor and a negligible affinity for estrogen, glucocorticoid and mineralocorticoid receptors [8,9].

Dienogest is very well absorbed and shows high bioavailability (~91%) after oral administration with peak serum concentrations are reached in 2 hrs. The half-life of dienogest is approximately 10 hrs. There is no risk of accumulation after repeated dosing due to shot half life [10]. Like other progestogens, Dienogest, are metabolized mainly by thecytochrome P450 (CYP3A4) system.

Dienogest has beenthoroughlyinvestigated for the treatment of endometriosisby two independent clinical trialsin Europe and Japan, which included dose-range, placebo-controlled, active comparator-controlled and long-term studies. Dienogest has also been studied extensively in other countries also.

Dienogest suppresses ovulation which then causes down regulation of endometrial cell proliferation. Hyperprogesteronic and hypoestrogenic environment causes decidualisation of this ectopic endometrium, which later atrophies due to continued altered endocrinal environment. Anti-inflammatory activity of dienogest by alteration of proinflammatory markers has also been demonstrated in various *in vitro* and *in vivo* clinical experiments.

How Eeffective is Dienogest

a. *Comparison with placebo:* In a European study, Dienogestwas compared against placebo by Strovitzki [11]and reduction in Visual Analogue Score, for pain as well as reduction in bowel and bladder symptoms were seen; improvement in quality of life was also noted, more in dienogest group.

b. *Comparing Dienogest with GnRH Agonists*: Strovitzki [11] compared Dienogest against Leuprolide acetate (long acting GnRH analogue) in endometriosis. The primary efficacy variable was the absolute change inendometriosis-associated pelvic pain.He also assessed Biberoglu and Behrman (B&B) severity profile, encompassing symptoms (pelvic pain, dysmenorrhoea and dyspareunia) and physical findings (pelvic tenderness and induration) [12] and Quality of life using the Short Form-36TM (SF-36) Health Survey.

Though improvement was comparable in both groups, side effects in both groups was different. Headache was the most common complaint reported by women in both the groups. Women receiving leuprolidealsp faced hot flushes, which can be explained by hypo- oestrogenemia caused by GnRH agonists. Infrequent bleeding was noted in this group whereas prolonged bleeding was a common finding in Dienogest group, but after some time,both the groups had amenorrhoea. Weight gain and rise in blood pressure was not seen in dienogest group, buta woman developed severe depression in dienogest group. Estrogen levels remained stable in women ondienogest, lipid profilealso remained normal. Marker of bone formation, serum bone-specific

alkalinephosphatase levels increased and markers of bone resoptionurine calcium/ creatinine decreased in Dienogest and increased in LeuprolideAcetate group, indicating an adverse effect with Leuprolide acetate on bone health.

Another multicentric study was conducted by the same author [13] to analyze the secondary efficacy and safety outcomes of dienogest. Approximately half of women were free of any pain. Significant reduction was noted in dysmenorrhoea and dyspareunia, but 1% women in Dienogest group and 2% in Leuprolide Acetate group still had severe symptoms. Significant reduction in pelvic tenderness and induration was seen.Improvement was more evident from 4 weeks, i.e. the first follow up.

Womenwho received Dienogest, were moreproductive at work, had higher energy levels, and were less limited insocial activities. These data indicate that DNG provides additional quality of lifebenefits relative to LeuprolideAcetate [13,14], which may help to limit the impact of endometriosison daily life.

This drug was compared with other GnRH analogues; Harada et al [15] and Cosson M [16] compared Dienogest with intranasal Buserelinand Triptorelinin women with endometriosis. Results are consistent with other studies provingDienogest at par with these GnRH agonists in controlling most of the signs and symptoms of endometriosis.

Hence, Dienoget is comparable to GnRH agonists in endometriosis and has advantagesover GnRH treatment as far as safety and tolerability is concerned.

c. What is the optimal dose of Dienogest?

Studies by Harda&Momoeda [15,16] have investigated Dienogest at doses of 1 mg, 2 mg, and 4mg [32] daily. 2 mg and 4 mg daily doses were equal in efficacy, andsafety. Higher reductions in estradiol levels were associated with the 4 mg dose; this indicated that 2 mg daily may offer maximum benefit without antiestrogenic effect on bone mineral density. Unsatisfactory bleeding patterns were observed at dose of 1 mg/day [17] At dose of 2mg/day, E2 levels reduced in most cases(<60 pg/mL) but in some patients E2 levels of 120 pg/mL were seen and there was follicular growth without ovulation. In such patient higher doses of Dienogest may be useful, specially 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. At a dose of 2mg it also inhibits ovulation in most women.

Even at higher dosesof 20mg/dayDienogest has almost negligible impact on haemostasis, thyroid and adrenal function, glucose and lipid metabolism, liver function, electrolyte balance and haematology [18,19].

Although small increase in the prothrombin fragment,antithrombin III and protein C have been noted. There was improvement in HDL levels.

This is in contrast to other older progesterons specially MedroxyProgesterone Acetate which increases LDL, TG, total and free cholesterol, and decreases HDL and reduce levels of apolipoprotein A1. MPA also reduced glucose toleranceand increased insulin resistance.

Dienogest at 2mg/day inhibits ovulation.[21] However, ovulation may not be prevented by 1 mg dose. There is moderate suppression of estrogen levels after Dienogest.

It fits estrogen threshold hypothesis which proposes that the optimal endometriosis therapy should provide a suppression of estrogen levels sufficient to inhibit endometrial stimulation

d. Are There Any Effect after Long Term Administration

Petralgia [22] administered Dienogest 2mg/day for 53 weeks in women who completed 12 weeks of therapy with dienogest as a part of pilot project. A subset of women was evaluated in a 24-week follow-up after treatment discontinuation. Progressive decrease in VAS score was noticed with no or minimal changes in laboratory parameters and body weight. In fact decrease in endometriosis associated pelvic pain persisted even for 24 weeks after leaving treatment.

The observation of prolonged pain relief even after the return of normal menses suggests a sustained effect on endometrial lesions. This can be explained by reduction in endometrial lesions. Irregular PV bleeding may occur but if woman are properly councelled, there is better compliance for this drug.

Dienogest also has effect in adenomyosis and chocolate cyst; in a study conducted in Japan by Sujimoto [23]. He reported significant decrease in size of chocolate cyst, myometrialthickess also decreased; but these effects were short term, and increase in size of chocolate cyst and myometrial thickness occurred on stopping treatment.

Sexual improvement in terms of female sexual dysfunction (FSD), and self-administered Female Sexual Function Index (FSFI) and on Female Sexual Distress Scale (FSDS) also improves [24,25].

e. Adverse Effects

Dienogest, is not free of side effects, although it is close to ideal drug for the treatment of endometriosis. The most frequently reported adverse effects are irregular PV bleeding, headache, acne, nausea, weight gain, breast tenderness, depressed mood and flatulence. Cause of atypical genital bleeding is probably breakthrough bleedingof pseudo-decidualized endometrium 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.

f. Can Dienogest be given with Estrogen for Treatment of Endometriosis?

Dienogest has been traditionally used along with estrogen as a contraceptive. A recent study [26] retrospectively compared the impact ofpost operativeestradiol valerate + dienogest (Group A) or Levonorgestrel-releasing uterine device (LNG-IUD) (Group B) in women undergoing surgery for peritoneal endometriosis, ovarian endometrioma, or excision of rectovaginal septum nodules. They reported a significant decrease in VAS score and Ca-125 levels ($P<0.05$) at 12 and 24 months. Relapse ratewas slightly lower in Dienogest group. Treatment satisfaction which was assessed bythe percentage of women who completed their treatment, without requiring suspension of the assigned regimen was more in LNG IUS group.It can be explained by one time application of LNG- IUS and comparatively lower cumulative cost.

A Multicentre RCT [27] compared combination of Estradiol valerate and Dienogest with GnRH analogue given post operatively. Both drugs were equally effective but Dienogest had better tolerability and side effects profile.GnRH analogues, had significant difference in vasomotorsymptoms, decreased libido and discomfort due to amenorrhea, undesired effects on bone mineral density and climactericsymptoms were observed.

g. Dienogest versus Norethindone

Norethindroneacetate, a drug approved by the U.S. Food and DrugAdministration and the Italian Ministry of Health for thetreatment of endometriosis was compared to Dienogest.

Vercellini [28] compared the long used drug Norethindrone acetate 2.5 mg/day with Dienogest 2mg/day. Pain profile and abnormal bleeding profile were similar in both groups. Dienogest had better tolerability. There was no difference in health-related quality of life or sexual functioning. Norethindrone had better effect on psychological profile and better scoring on depression scale compared to Dienogest. This may be due to androgenic effect of Norethindrone which is lacking in Dienogest [29,27].

Both groupsreported decreased libido and weight gain more commonly in Norethindrone group. Dienogest is costlier than Norethindrone which was one of the major reason for some women in Dienogest group discontinued it.

Other Newer Treatment Options for Medical Management of Endometriosis

1. Levonorgestrel Intrauterine device (LNG – IUD)

The use of the Levonorgestrel-releasing intrauterine system for postoperative treatment in endometriosis was first reported in1999 by Vercellini et al [30]. Levonorgestrel-releasing intrauterine device contains 52 mg of Levonorgestrel and releases 20 mcg of the drug every day over 5 years. Local action predominates in LNG-IUS, so systemic effects are less; hence less progesterone induced side effects, this leads tobetter patient tolerability. LNG-IUS is effective, especially in rectovaginal diseasebut it has not been approved by US-FDA for the treatment of endometriosis. However, there is some evidence of removal of LNG IUS due unacceptable irregular bleeding, persistent pain, or weight gain

Prasong Tanmahasamutet al [31] conducted a double-blind randomized controlled trial on 55 patients with endometriosis undergoing laparoscopic conservative surgery, who were randomized to a Levonorgestrel intrauterine system or expectant management group. Both groups showed improvement indysmenorrhoea and chronic pelvic pain. In LNG IUS group dyspareunia and quality of life also improved. When applied after laproscopic surgery, improvement was observed in all patients.

Comparison

a. LNG-IUS was compared to Inj DMPA; Wong et al [64] compared LNG IUS with DMPA for efficacy, recurrence and patients tolerance over a period of 3 years. There was improvement in both the groups but without much difference, however bone loss was observed in DMPA group which was not seen in

LNG IUS group putting this system at an advantage.

b. LNG IUS and GnRH agonist have similar improvement in pain scores and quality of life, with predominant amenorrhoea and postmenopausal symptoms in GnRH groups and irregular PV bleeding in LNG IUS group [32,33].

2. Etonogestrel& DMPA

Etonogestrelimpant has been used as contraceptive, intra-dermally in the arm, offering 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.

A RCT [34] compared the therapeutic efficacies of depot medroxyprogesterone acetate (DMPA) and Implanon with regard to pain relief, bleeding pattern and satisfaction. Improvement in pain score noted in both groups, more in Implanon, however significant difference($p<0.36$) was not seen. Like other studies evaluating progesterone, most effect was noticed in 3 month and not much change in VAS score after 6 months. Side effects in form of acne, loss of hair, weight gain, breast tenderness and prolonged PV bleeding were side effects commonly observed inboth treatment groups. 2 patients(10%) in DMPA group had severe depression after treatment. Implanon may be having a slight impact on carbohydrate metabolism.

Although DMPA therapy is effective in reducingendometriosis-associated pelvic pain, it is often accompaniedby unintentional weight gain, loss of libido, acne andreversible bone loss, which might adversely affect awoman's quality of life and preclude long-term use [69,70].

Another study mentions the impact on metabolism during Implanon and DMPA use. Impanon was found to have only a slight impact on carbohydrate metabolism [36].

DMPA increases LDL, triglyceride & cholesterol levels and decreases HDL and apolipoprotein A1

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

3. Cyproterone Acetate

A synthetic oral progestin, Cyprotore Acetate with an anti-androgenic effect, mediated by a competitive inhibition on the cytoplasmic testosterone receptor and a negative feedback effect on the hypothalamo-pituitary-ovarian axis. This drug is commonly used in patients with hirsutism. Although this drug is widely used off-label for the treatment of symptomatic endometriosis, the literature supporting the use in this indication is limited.

Vercellini [37] compared low-dose cyproterone acetate with a continuous monophasic oral contraceptive to treat recurrent pelvic pain after conservative surgery for symptomatic endometriosis. The parameters evaluated were pain, health-related quality-of life, psychoemotional status, and sexual functioning. Both were similarly effective in reducing recurrent pelvic pain after conservative surgery for endometriosis. Although the differences in the eight health-related quality-of-life score variations observed between the two study groups were limited, patients in the Cyproterone Acetate group reported slightly better health.

Many more drugs are being evaluated for the treatment of this condition and we hope that in future these newer drugs will be treating the root cause of endometriosis without having any side effects

Conclusion

Endometriosis is a chronic, debilitating & progressive condition, it demands thorough evaluation of the need of patient and case selective decision. Many cases of endometriosis are associated with infertility and most of the drugs used also 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 &post operativetreatment.

Dienogestholds a promising future for patients with endometriosis. Studies have compared Dienogestto GnRH agonists, Depot Medroxy progesterone Acetate, Norethindrone, and oral contraceptives. Good efficacy and tolerability was observed with minimal side effects and improved acceptance rate for this drug.

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 life

long condition, there are concerns about prolonged treatment with Dienogest. 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 are another good option in long term management of endometriosis without compromising compliance.

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