AUSTRALASIAN MENOPAUSE SOCIETY
EMPOWERING MENOPAUSAL WOMEN

**Information Sheet**

# Endometriosis – management after menopause

**Key Points**

- Medical management with either the combined oral contraceptive pill or treatments that create a hypo-oestrogenic state are used in premenopausal women.
- Evidence is sparse but current recommendations favour continuous combined oestrogen- progestogen preparations instead of unopposed oestrogens for women with a history of substantial endometriosis even after hysterectomy.
- Loss of oestrogen either through medical management or surgery has implications for both bone and cardiovascular health.

## Endometriosis

There is no unifying theory for the pathogenesis of endometriosis. The theory of retrograde menstruation was proposed in 1920 and is supported by the finding of higher rates of endometriosis in women with outflow obstruction. However, menstrual blood is often seen in the pelvis in women without endometriosis, so there must be other factors contributing. There is a familial pattern to endometriosis and a high concordance in monozygotic twins. Genetic studies have identified several candidate genes which predispose to endometrial cell survival and inhibition of cell apoptosis. Hormonal factors include increased oestrogen responsiveness in endometriosis with up-regulation of aromatase compared with normal endometrial tissue. Defective immune clearance of ectopic endometrial tissue and increase in inflammation also contribute (1).

## Premenopausal management of endometriosis

Historically, the oral contraceptive pill (OCP) with higher doses of ethinyl oestradiol has been first-line therapy, but even low-dose OCPs decrease pain more significantly than placebo. Continuous OCPs decrease recurrence rates of dysmenorrhea after surgical therapy when compared with cyclic OCPs. Continuous progestin administration either orally, by depot, or even as the levonorgestrel IUD, has been effective vs placebo. GnRH analogue (GnRHa), GnRH antagonist (GnRHant) and aromatase inhibitors (AI) therapy create a hypo-oestrogenic state and have been used to treat endometriosis. GnRHa is very effective but, as well as hypo-oestrogenic symptoms, has been associated with marked bone loss. AIs are



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second-line treatment. They decrease oestrogen production by aromatase but in premenopausal women may be associated with increased gonadotrophin drive to the ovary and are therefore used in combination with GnRHa or after oophorectomy (2). These measures for control of endometriosis have relevance for bone health in women approaching the menopause.

Since endometriosis inevitably returns after surgical extirpation or on cessation of medical therapy, current recommendations for the premenopausal treatment of endometriosis are to use ongoing medical treatment to treat pain and control endometrial growth, and to avoid recurrent surgery until surgery is needed to facilitate fertility. Definitive surgery which usually includes hysterectomy and bilateral oophorectomy can then be reserved for after completion of family (3, 4).

**Postmenopausal patients with a history of endometriosis**

It is apparent that oestrogen exposure is a stimulus to endometriosis growth (5). Menopause, either natural, or surgically or medically induced relieves endometriosis related symptoms. However, one cannot attribute this solely to a fall in circulating blood oestradiol. Follicular fluid released directly into the pelvis at the time of ovulation contains 4000 to 5000 times the concentration of oestradiol of that which is measured in the blood (6). Moreover, OCPs which contain oestrogen and progestin are often effective in controlling endometriosis in premenopausal women. Therefore, it is prevention of ovulation by oophorectomy or medically, as in OCP use, or naturally by menopause, that has the major impact on the treatment of endometriosis.

**Risk of recurrence of endometriosis with menopausal hormone therapy**

The evidence for safety or lack thereof of menopausal hormone therapy (MHT) is very sparse (7, 8). Gemmell et al reviewed the evidence for menopausal management in the setting of a history of endometriosis (9). They found only 32 case reports/series including 42 patients. Of these, 36 patients had had surgical menopause and 2 patients with natural menopause underwent subsequent bilateral oophorectomy.

Recurrence of endometriosis was reported in 17 case reports. Of these, 12 patients with prior hysterectomy were taking oestrogen alone (some in high dose). Four patients were taking cyclical oestrogen plus progestogen therapy, and in one case the combined oestrogen-progestogen regimen is not specified. The majority of patients had had extensive endometriotic disease pre MHT. The only clinical trial of unopposed oestrogen vs oestrogen + progestogen therapy was small and underpowered to show a statistically significant increase in risk of recurrence of endometriosis with unopposed oestrogen (RR 7.24, CI 0.40, 130.54) (10).



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**Malignant transformation of endometriotic deposits**

Twenty case reports and series of malignant transformation of endometriotic foci in postmenopausal women with a history of endometriosis on HRT have been identified (n=25). Unopposed oestrogen was used in all but 1 patient, with the addition of testosterone in 4 patients. Two patients had the addition of progestogen after some years on unopposed oestrogen and 1 patient took cyclical progestogen. Endometrioid adenocarcinoma was by far the most commonly diagnosed MHT-associated malignancy in patients with a history of endometriosis (n = 18). Leiserowitz et al reported a second series of 10 patients with extragonadal endometriosis-related malignancy (11). Nine of these women were postmenopausal, with 6 women reported to have taken unopposed oestrogen.

There has been one case report of recurrence and malignant transformation of endometriosis associated with highly-concentrated soy isoflavone supplement use and the safety of phytoestrogens in this patient population is therefore unclear (9).

Although the evidence remains sparse and case reports of recurrence or malignant transformation are few, current recommendations favour continuous combined oestrogen-progestogen preparations instead of unopposed oestrogens for women with a history of substantial endometriosis even after hysterectomy, especially if there has been extensive disease.

**Implications for post-menopausal bone and cardiovascular health**

The premenopausal treatment of endometriosis involves reducing the oestrogen effect on endometriotic tissue, usually by preventing ovulation, by GnRH analogues, or by early oophorectomy leading to premature menopause. This has implications for postmenopausal bone and cardiovascular health. Premenopausal oestrogen loss from any cause is associated with impaired bone density accrual or early bone loss (12). Endometriosis has been also associated with an increase in cardiovascular risk and disease by at least two distinct mechanisms (13). First, early menopause and loss of oestrogen, either through surgery or through medical management, has been shown to be associated with increased cardiovascular risk. Secondly, both endometriosis and atherosclerosis share risk insofar as they are both diseases of inflammation.

Therefore, the menopausal patient with a history of endometriosis presents a particular challenge in managing menopausal symptoms, bone health and prevention of cardiovascular risk.

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