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Induced menopause in women with endometriosis

Endometriosis and menopausal symptoms

Endometriosis is a common condition affecting women of reproductive age. It can be very painful and debilitating. Women with endometriosis may be treated medically, surgically or with lifestyle changes to help control the symptoms and severity of the disease. Some of the treatment offered can induce a menopause-like state, leading to a variety of symptoms ranging in severity. There is evidence to suggest that providing women with information of what to expect can reduce their psychological and physical morbidity (NICE Quality Standards[1]).

Why does inducing menopause help the symptoms of endometriosis?

Endometriosis can develop when deposits of endometrium exist outside the uterine cavity, they can then be stimulated and bleed with every cycle. By suppressing the menstrual cycle, the symptoms may resolve. Inducing menopause will stop ovarian cyclical activity and hence cyclical stimulation of endometriotic deposits.

The methods of inducing menopause are:

- Gonadotrophin releasing hormone agonists: these downregulate the pituitary gland and lower estrogen levels to within the menopausal range. They induce amenorrhoea and often menopausal symptoms.
- Surgery involving bilateral oophorectomy: this may be with or without a hysterectomy but will permanently induce menopause. The loss of libido is often more marked with a surgically induced menopause.

Why is Hormone Replacement Therapy (HRT) important in managing women with an induced menopause?

- Women with an induced or surgical menopause due to endometriosis are usually younger women, below the age of natural menopause. The loss of estrogen can predispose them to osteoporosis and cardiovascular disease. HRT has been shown to be protective for both of these factors.[2]
- Distressing symptoms such as vasomotor, cognitive and genitourinary can be alleviated by adequate HRT.
- Lack of libido is caused by the low estrogen state and loss of testosterone particularly in women with a surgical menopause.

What are the key points for managing women with endometriosis who have induced menopause?

- Offer HRT to all women unless there is a specific contraindication, e.g. hormone sensitive breast cancer, and continue it until at least the age of natural menopause.[3]
- Women with induced menopause or surgical menopause are often younger than the natural age of menopause and may be relatively uninformed about what to expect from menopause. Education is therefore important.

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- Recognise that sudden onset of menopausal symptoms can be very distressing and difficult to cope with.
- Giving add-back HRT for those women with pharmacologically induced menopause is important for bone and cardiovascular protection and should improve patient compliance.[2]
- Younger women often need higher doses of estrogen to relieve their symptoms.
- HRT is not a contraceptive and adequate contraception is still required. HRT can be provided with the combined oral contraceptive pill.
- Continuous combined estrogen/progesterone HRT regimes should be used for women with a uterus and this can include estrogen in conjunction with a hormone releasing IUD.
- For hysterectomised women with endometriosis it is advised that continuous combined HRT is used in preference to estrogen alone as there is some evidence that estrogen only HRT may increase the risk of recurrence of pain over time and there is also a very small risk of malignant transformation. For these reasons it may be safer to maintain patients on a continuous combined regimen.[3,4] This may later be changed to estrogen alone, due to a possible better safety profile in women over the age of natural menopause, but this needs to be balanced with the theoretical risk of reactivation and malignant transformation of any residual endometriosis, which can occur many years later. It is generally recommended that ccHRT is continued instead of estrogen alone, but this must be balanced with the individual's risk of breast cancer. A pragmatic approach assessing the degree of extra uterine disease at the time of hysterectomy may be used to guide practice.
- Testosterone may be used for relieving symptoms of hypoactive sexual desire disorder (HSSD), however there are no randomised controlled trials in women having had a surgical menopause due to endometriosis.

What are the common symptoms women can experience in induced menopause?

The symptoms women experience are wide ranging but they may include:

- Vasomotor symptoms, including hot flushes and night sweats
- Musculoskeletal symptoms, including joint and muscle pains
- Low or changed mood and loss of libido
- Memory loss and anxiety
- Genitourinary symptoms, including vaginal dryness and recurrent urinary tract infections
- Hair loss

What are the non-pharmacological options for management of symptoms of the menopause for women with induced menopause?

- Regular exercise
- Weight management
- Cognitive Behavioural Therapy

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What are the pharmacological options for management of menopausal symptoms for women with induced menopause?

- HRT is the first line treatment both for women after surgical menopause and as add-back therapy for those women receiving medical therapy which induces menopause.
- The evidence is uncertain about how soon to start HRT after induced menopause. For those on GnRH analogues, clinicians are recommended to commence add-back HRT with the start of GnRH agonist therapy to prevent bone loss and hypo-estrogenic symptoms.[3] For those with a surgical menopause, there is no clear consensus on the ideal interval to start hormonal therapy post surgery. A decision should be made after discussion with the patient regarding the risk of reactivation of the endometriosis versus the sudden onset of menopausal symptoms.
- Continuous combined estrogen/progesterone HRT or Tibolone can be used for women regardless of whether they have had surgery to remove their womb or not.[4]
- For women with low libido, Tibolone may be helpful as it provides estrogen, progestogen and some androgenic activity. An alternative may be to prescribe testosterone alongside continuous combined HRT.
- Women with genitourinary symptoms such as dryness and dyspareunia may benefit from vaginal estrogen in the form of vaginal tablets or cream and these can be safely prescribed with or without concurrent systemic HRT. Vaginal DHEA can be used as an alternative in women in whom estrogen is not optimally effective.
- Women may benefit from concurrent management of underlying depression or anxiety.
- Discuss with women that over-the-counter medications can help menopausal symptoms but safety is uncertain and they can interact with other medications. They are unlikely to offer bone or cardiovascular protection.[4]

Is there a risk of worsening endometriosis on add-back HRT?

The estrogen threshold theory suggests that add-back HRT or HRT after removal of the ovaries contains a low enough dose of estrogen for maintenance of bone density and relief of hypoestrogenic and vasomotor symptoms, but not enough to reactivate endometriosis.

Is there a risk of reactivating endometriosis after oophorectomy on HRT and is there a risk of reactivated endometriosis transforming into cancer?

There is little high-quality data to answer these questions so the absolute risk of disease reactivation and malignant transformation cannot be quantified[5], but it has occurred in the literature. However, existing evidence found no increased risk in malignant transformation after 6 years follow up between estrogen only and combined HRT regimes.[8] Consensus opinion is that for women after oophorectomy with little or no residual disease, treatment with HRT brings no or little extra risk of endometriosis recurrence or ovarian cancer. For women with significant residual disease, benefits of HRT may outweigh the risks if the woman is less than 45 years old at the age of menopause or if symptoms are severe.[5]

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Therefore, for women who still have their uterus, continuous combined HRT or Tibolone should be prescribed. For hysterectomised women with very little or no residual disease, estrogen only HRT could be considered, after initial therapy with continuous combined HRT, as it may have a better safety profile in women over the age of natural menopause. In general, ccHRT is preferred certainly for those with extensive peritoneal disease. This decision must be made on a case by case basis. If recurrence does occur these women should be referred to a specialist with an interest in menopause and investigated for malignant change if symptoms persist.

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Authors: Rosamund Malhas and Lynne Robinson in collaboration with the medical advisory council of the British Menopause Society

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