HRT for Premenopausal Women Undergoing Bilateral Salpingo-Oophorectomy for Benign Disease - Full Clinical Guideline

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Contents

1. Introduction

Women may elect to undergo bilateral salpingo-oophorectomy (BSO) prior to the menopause for a variety of benign indications including: endometriosis and/or chronic pelvic pain; recurrent ovarian cysts; severe, refractory pre-menstrual syndrome; and opportunistically at the time of hysterectomy performed for various gynaecological reasons, most commonly, dysfunctional uterine bleeding with or without a fibroid uterus.

Young women undergoing BSO will be rendered menopausal by virtue of their surgery. If untreated, they will experience all the typical symptoms of oestrogen deficiency, including: vasomotor symptoms such as hot flushes and night sweats; musculoskeletal symptoms, for example, joint and muscle pains and headaches; low mood, poor memory and concentration loss; urogenital symptoms i.e. vaginal dryness and urinary incontinence; and sexual difficulties such as reduced libido. As a consequence, their quality of life may be severely affected. When menopause occurs abruptly because of surgical removal of both ovaries, rather than there being a gradual decline in the level of circulating oestrogen and progesterone such as that which occurs during a natural menopausal transition, levels decrease immediately and hence symptoms of oestrogen deficiency are both more frequent and more severe following a surgical menopause (1).

In addition to the immediate symptoms of oestrogen deficiency, women rendered prematurely menopausal following BSO are at an increased risk of developing osteoporosis and cardiovascular disease in the future.

The new NICE guidance on the diagnosis and management of the menopause states that women who are likely to go through the menopause as a result of medical or surgical treatment should be offered information about the menopause before they have their treatment. Women should be made aware of the importance of starting hormonal replacement therapy (HRT) (unless contraindicated) and continuing treatment until at least the age of the natural menopause (2).

In a departmental audit of clinical practice between 1st January and 30th June 2016, only 58.3% of pre-menopausal women undergoing BSO for benign disease were given any information at all about the menopause and/or HRT and only 5.6% of women received this information prior to surgery. HRT was only prescribed for 13.9% of women.

2. Aim and Purpose

To inform clinicians of the importance of prescribing HRT to premenopausal women undergoing BSO for benign disease, to summarise the evidence regarding the risks and benefits of treatment as well as alternatives to treatment and the risks of no treatment and to provide guidance on what HRT formulations to prescribe and when.

3. Abbreviations

BMI	-	Body Mass Index
BSO	-	Bilateral Salpingo-Oophorectomy
CBT	-	Cognitive Behavioural Therapy
HRT	-	Hormone Replacement Therapy
SERM	-	Selective Estrogen Receptor Modulators
SNRI	-	Selective Noradrenaline Reuptake Inhibitors
SSRI	-	Selective Serotonin Reuptake Inhibitors
VMS	-	Vasomotor Symptoms
VTE	-	Venous Thromboembolism

4. HRT

Pre-menopausal women undergoing BSO for benign disease need information regarding the menopause and HRT pre-operatively so that they can make an informed decision about whether or not to proceed with their surgery. This is particularly important since the surgery they are contemplating is for benign, rather than malignant, disease i.e. the aim of surgery is to increase the quality of life rather than life expectancy. As with any consent process, the potential risks and benefits of treatment should be explained to women, as well as any alternative treatments and the consequences of no treatment (3).

4.1 Risks of HRT in Pre-Menopausal Women undergoing BSO for Benign Disease

There have been concerns previously regarding the risks of VTE, cardiovascular disease, diabetes and breast cancer associated with the use of HRT. Although data from the Women's Health Initiative studies on HRT raised some safety issues, their observations cannot be applied to women experiencing a premature menopause as women in those studies were all post-menopausal (4).

The risk of VTE is increased by oral HRT compared with the baseline population risk but the risk associated with transdermal HRT given at standard therapeutic doses is no greater than the baseline population risk. Transdermal rather than oral HRT should be considered for women who are at increased risk of VTE, including those with a BMI over 30kg/m^2.

HRT does not increase the risk of cardiovascular disease when started in women under the age of 60.

There is a small increase in the risk of stroke in women taking oral (but not transdermal) HRT but the baseline population risk of stroke in women under the age of 60 years is very low.

HRT is not associated with an increased risk of developing non-insulin dependent diabetes mellitus, nor has it been found to increase the risk of breast cancer in women when started before the age of natural menopause (5-7). Beyond the age of 50, there is a slight increase in the risk of breast cancer in women taking combined HRT. This risk is related to the duration of treatment (beyond the age of the natural menopause) and reduces after stopping treatment. HRT with oestrogen alone is associated with little or no change in the risk of breast cancer.

Progestogen should be given in combination with oestrogen therapy to protect the endometrium in women who have not had a hysterectomy. Unopposed oestrogen in this group of women significantly increases the risk of endometrial cancer.

4.2 Benefits of HRT in Pre-Menopausal Women undergoing BSO for Benign Disease

Women should be made aware of the importance of starting HRT (unless contraindicated) and continuing with treatment until at least the age of the natural menopause (2). HRT is useful for the:

- Treatment of symptoms associated with oestrogen deficiency

Symptoms of oestrogen deficiency include VMS such as hot flushes and sweats, musculoskeletal symptoms, for example, joint and muscle pain, effects on mood, urogenital symptoms i.e. vaginal dryness and sexual difficulties. HRT is indicated for the treatment of all of these symptoms of oestrogen deficiency (8-10). Vasomotor symptoms respond rapidly to systemic HRT.

- Prevention of disease associated with long-term oestrogen deficiency

Exogenous oestrogens have been shown to have beneficial effects on cardiovascular status and bone density. They increase the levels of cardioprotective high-density lipoproteins and decrease total cholesterol and low-density lipoproteins (15). Some data show that HRT use before the age of 60 years results in a 24% reduction in coronary artery disease and a 30% decrease in total mortality (11).

Oestrogen replacement has been shown to have beneficial effects on bone mineral density in women following premenopausal BSO (12-14). HRT may help alleviate low mood that arises as a consequence of the menopause and may also reduce the possible risk of cognitive impairment.

4.3 Alternatives to HRT in Pre-Menopausal Women undergoing BSO for Benign Disease

Non-hormonal treatment of menopausal symptoms can be considered for women with contraindications to HRT (15), for example clonidine, SSRIs, SNRIs and CBT. There is some evidence that herbal remedies such as isoflavones and black cohosh may relieve VMS but their efficacy is unproven and their safety uncertain. CBT may help alleviate low mood or anxiety that arises as a result of the menopause.

Whilst the above measures may help alleviate some of VMS associated with the menopause, none help in the prevention of disease associated with long-term oestrogen deficiency. General measures to reduce cardiovascular risk factors and avoid bone loss such as physical activity, maintaining a healthy weight, a calcium rich diet, vitamin D supplementation and avoidance of smoking and alcohol should be discussed with all women but especially those who decline HRT. Pharmacological treatments for bone protection other than HRT, for example, bisphosphonates, SERMs, bazedoxifene, raloxifene, tamoxifen and teriparatide, should only be considered with advice from osteoporosis specialists.

4.4 Consequences of no HRT in Pre-Menopausal Women undergoing BSO for Benign Disease

Young women who have had a BSO and are not treated with HRT are at an increased risk of osteoporosis, coronary heart disease and cardiovascular accidents (16). Prolonged oestrogen deficiency also has a significant impact on psychological wellbeing and quality of

life (17-20). There is some evidence to suggest that surgical menopause may, when untreated with oestrogen replacement, result in an increased risk of Parkinson's disease (21) and cognitive impairment/dementia risk (22, 23). Moreover, the longer the duration of oestrogen deficiency, the more severe the consequences (15). Prolonged oestrogen deficiency prior to the age of the natural menopause is associated with reduced life expectancy (7, 24-27).

5. Pre-menopausal Women undergoing BSO for Benign Disease

5.1 Women who have had BSO without Hysterectomy

- Commence a continuous combined patch (e.g. Evorel Conti) on day 1 post-op
- Can covert to continuous combined oral preparation (e.g. Kliofem) after 6 weeks if preferred

5.2 Women who have had BSO with Hysterectomy

- Commence oestrogen only patch (e.g. Estradot 50) on day 1 post-op
- Can covert to oestrogen only oral preparation (e.g. Elleste Solo) after 6 weeks if preferred

5.3 Women who have had BSO and Hysterectomy for Endometriosis

If significant residual disease

- Commence continuous combined patch (e.g. Evorel Conti) on day 1 post-op
- Can covert to continuous combined oral preparation (e.g. Kliofem) after 6 weeks if preferred
- Can convert to oestrogen only preparation (e.g. Elleste Solo or Estradot 50) after 6 months

If no significant residual disease

- Commence oestrogen only patch (e.g. Estradot 50) on day 1 post-op
- Can covert to oestrogen only oral preparation (e.g. Elleste Solo) after 6 weeks if preferred

As the risk of VTE associated with transdermal HRT given at standard therapeutic doses is no greater than the baseline population risk, women commenced on transdermal HRT immediately postoperatively do not require anticoagulation unless there are other risk factors for VTE, for example: surgical procedure with a total anaesthetic and surgical time of more than 60 minutes; known thrombophilia; BMI >30kg/m2; significant medical comorbidity e.g. heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases, inflammatory conditions; and personal or family history (in a first degree relative) of VTE.
Initially women usually require a moderate dose (oral oestradiol, commonly 2mg/day or a transdermal patch of 100µg) to overcome the systemic adverse effects of oestrogen deficiency and to oestrogenise the vaginal epithelium fully (15). All women commenced on HRT should be reviewed by their general practitioner after three months and annually thereafter until the age of 50, when the risks and benefits of HRT should be reassessed. No routine monitoring tests are required but may be prompted by specific symptoms or concerns, for example, unscheduled bleeding.

Local oestrogens are effective in the treatment of urogenital symptoms (28-31). Clinicians should be aware that despite seemingly adequate systemic HRT, women may still experience symptoms such as vaginal dryness and superficial dyspareunia. Topical oestrogens may be given in addition to systemic HRT (31); they carry very little risk and can be continued indefinitely. Suitable regimens include Ovestin daily for two weeks then twice weekly thereafter or Vagifem 10mg twice weekly. Symptoms of urogenital atrophy often recur when treatment is stopped. Although adverse effects from vaginal oestrogens are very rare, any unscheduled bleeding should be reported. It is not necessary to routinely monitor endometrial thickness. Moisturisers e.g. Replens MD™ and lubricants e.g. Yes WB™ can be used alone or in addition to vaginal oestrogens.

Androgen replacement should be considered even with normal adrenal function because loss of ovarian activity can reduce androgen production by 50% which can have profound effects on general and sexual wellbeing (15). Following BSO, in addition to standard HRT, young women may therefore also benefit from testosterone replacement, especially if they continue to complain of low energy levels and reduced libido after they have been adequately oestrogenised. Women contemplating testosterone replacement should be informed that data regarding its long term efficacy and safety is limited (38-46). If androgen therapy is commenced, its treatment effect should be evaluated after 3-6 months and possibly be limited to 24 months. Recommended formulations include Testim gel or Testogel (one tube or sachet to last 7 days).

6. Contraindications to HRT

HRT is generally contraindicated in breast cancer survivors. The following however are not contraindications to HRT: women carrying the BRCA1/2 gene mutation but without personal history of breast cancer after prophylactic BSO; migraine with/without aura; hypertension; obesity; and fibroids. Transdermal preparations may be preferable for: women with worsening migraine symptoms on systemic HRT; women with focal migraines; hypertension; women at increased risk of VTE; women who are overweight or obese. If there is any doubt about whether HRT is contraindicated, advice from a specialist with expertise in the menopause should be sought, ideally pre-operatively, so that a plan can be finalised prior to the onset of any symptoms.

7. Monitoring Compliance and Effectiveness

As per agreed Business unit audit forward programme

8. References

1. Benshushan A, Rojansky N, Chaviv M, Arbel-Alon S, Benmeir A, Imbar T, et al. Climacteric symptoms in women undergoing risk-reducing bilateral salpingo-oophorectomy. Climacteric : the journal of the International Menopause Society. 2009;12(5):404-9.
2. Sarri G, Davies M, Lumsden MA, Guideline Development G. Diagnosis and management of menopause: summary of NICE guidance. Bmj. 2015;351:h5746.
3. Pokoradi AJ, Iversen L, Hannaford PC. Factors associated with age of onset and type of menopause in a cohort of UK women. American journal of obstetrics and gynecology. 2011;205(1):34 e1-13.
4. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. Jama. 2002;288(3):321-33.
5. Benetti-Pinto CL, Soares PM, Magna LA, Petta CA, Dos Santos CC. Breast density in women with premature ovarian failure using hormone therapy. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology. 2008;24(1):40-3.
6. Soares PM, Cabello C, Magna LA, Tinois E, Benetti-Pinto CL. Breast density in women with premature ovarian failure or postmenopausal women using hormone therapy: analytical cross-sectional study. Sao Paulo medical journal = Revista paulista de medicina. 2010;128(4):211-4.
7. Wu X, Cai H, Kallianpur A, Li H, Yang G, Gao J, et al. Impact of premature ovarian failure on mortality and morbidity among Chinese women. PloS one. 2014;9(3):e89597.
8. Madalinska JB, van Beurden M, Bleiker EM, Valdimarsdottir HB, Hollenstein J, Massuger LF, et al. The impact of hormone replacement therapy on menopausal symptoms in younger high-risk women after prophylactic salpingo-oophorectomy.

Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2006;24(22):3576-82.
9. Piccioni P, Scirpa P, D'Emilio I, Sora F, Scarciglia M, Laurenti L, et al. Hormonal replacement therapy after stem cell transplantation. Maturitas. 2004;49(4):327-33.
10. Absolom K, Eiser C, Turner L, Ledger W, Ross R, Davies H, et al. Ovarian failure following cancer treatment: current management and quality of life. Human reproduction. 2008;23(11):2506-12.
11. Rossouw JE, Prentice RL, Manson JE, Wu L, Barad D, Barnabei VM, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. Jama. 2007;297(13):1465-77.
12. Prior JC, Vigna YM, Wark JD, Eyre DR, Lentle BC, Li DK, et al. Premenopausal ovariectomy-related bone loss: a randomized, double-blind, one-year trial of conjugated estrogen or medroxyprogesterone acetate. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 1997;12(11):1851-63.
13. Lindsay R, Hart DM, Forrest C, Baird C. Prevention of spinal osteoporosis in oophorectomised women. Lancet. 1980;2(8205):1151-4.
14. Crofton PM, Evans N, Bath LE, Warner P, Whitehead TJ, Critchley HO, et al. Physiological versus standard sex steroid replacement in young women with premature ovarian failure: effects on bone mass acquisition and turnover. Clinical endocrinology. 2010;73(6):707-14.
15. Arora P, Polson DW. Diagnosis and management of premature ovarian failure. The Obstetrician & Gynaecologist. 2011;13(2):67-72.
16. Oliver MF, Boyd GS. Effect of bilateral ovariectomy on coronary-artery disease and serum-lipid levels. Lancet. 1959;2:690-4.
17. Liao KL, Wood N, Conway GS. Premature menopause and psychological well-being. Journal of psychosomatic obstetrics and gynaecology. 2000;21(3):167-74.
18. Schmidt PJ, Luff JA, Haq NA, Vanderhoof VH, Koziol DE, Calis KA, et al. Depression in women with spontaneous 46, XX primary ovarian insufficiency. The Journal of clinical endocrinology and metabolism. 2011;96(2):E278-87.
19. Mann E, Singer D, Pitkin J, Panay N, Hunter MS. Psychosocial adjustment in women with premature menopause: a cross-sectional survey. Climacteric : the journal of the International Menopause Society. 2012;15(5):481-9.
20. Mann E, Smith MJ, Hellier J, Balabanovic JA, Hamed H, Grunfeld EA, et al. Cognitive behavioural treatment for women who have menopausal symptoms after breast cancer treatment (MENOS 1): a randomised controlled trial. The Lancet Oncology. 2012;13(3):309-18.
21. Rocca WA, Bower JH, Maraganore DM, Ahlskog JE, Grossardt BR, de Andrade M, et al. Increased risk of parkinsonism in women who underwent oophorectomy before menopause. Neurology. 2008;70(3):200-9.
22. Rocca WA, Bower JH, Maraganore DM, Ahlskog JE, Grossardt BR, de Andrade M, et al. Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. Neurology. 2007;69(11):1074-83.
23. Bove R, Secor E, Chibnik LB, Barnes LL, Schneider JA, Bennett DA, et al. Age at surgical menopause influences cognitive decline and Alzheimer pathology in older women. Neurology. 2014;82(3):222-9.
24. Ossewaarde ME, Bots ML, Verbeek AL, Peeters PH, van der Graaf Y, Grobbee DE, et al. Age at menopause, cause-specific mortality and total life expectancy. Epidemiology. 2005;16(4):556-62.
25. Amagai Y, Ishikawa S, Gotoh T, Kayaba K, Nakamura Y, Kajii E. Age at menopause and mortality in Japan: the Jichi Medical School Cohort Study. Journal

of epidemiology. 2006;16(4):161-6.
26. Rocca WA, Grossardt BR, de Andrade M, Malkasian GD, Melton LJ, 3rd. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. The Lancet Oncology. 2006;7(10):821-8.
27. Hong JS, Yi SW, Kang HC, Jee SH, Kang HG, Bayasgalan G, et al. Age at menopause and cause-specific mortality in South Korean women: Kangwha Cohort Study. Maturitas. 2007;56(4):411-9.
28. Suckling J, Lethaby A, Kennedy R. Local oestrogen for vaginal atrophy in postmenopausal women. The Cochrane database of systematic reviews. 2006(4):CD001500.
29. Rubinow DR, Schmidt PJ, Roca CA. Estrogen-serotonin interactions: implications for affective regulation. Biological psychiatry. 1998;44(9):839-50.
30. Sarrel PM. Sexuality in the middle years. Obstetrics and gynecology clinics of North America. 1987;14(1):49-62.
31. Pacello PC, Yela DA, Rabelo S, Giraldo PC, Benetti-Pinto CL. Dyspareunia and lubrication in premature ovarian failure using hormonal therapy and vaginal health. Climacteric : the journal of the International Menopause Society. 2014;17(4):342-7.

Appendix A

Information sheet for pre-menopausal women undergoing BSO for benign disease

The leaflet aims to answer your questions about taking HRT after your operation. If you have any questions or concerns, please speak to the doctor or nurse caring for you.

What is the menopause?

You are about to have surgery to remove your ovaries. This is essentially going to make you go through the menopause. The menopause is when you stop having periods, which usually occurs around the age of 50.

Your ovaries produce hormones called oestrogen and progesterone. Oestrogen has several benefits for women: it protects the heart and helps strengthen the bones. Once you have had surgery to remove your ovaries, you will no longer produce oestrogen meaning that you will be at increased risk of developing heart disease and osteoporosis (thin bones) in the future.

Also, as you may be aware, women who go through the menopause experience symptoms such as hot flushes, night sweats, joint and muscle pains, headaches, low mood, poor memory, concentration loss, urinary incontinence, vaginal dryness and reduced sex drive.

When you go through the menopause naturally, the levels of oestrogen and progesterone in your blood gradually decline meaning that you are less likely to notice that the hormones aren't there anymore and less likely to experience the symptoms described above. When you have surgery to remove your ovaries, the levels of hormones in your blood fall abruptly, so the symptoms are usually much greater.

What can we do to help?

We can protect your heart and your bones and prevent the unpleasant symptoms of the menopause by giving you hormone replacement therapy, or HRT. We strongly recommend this. HRT is a way of managing the menopause by replacing the oestrogen that your ovaries would have naturally produced had you not had an operation to remove them.

Are there any risks of HRT?

You may have heard stories about the risk of breast cancer, heart disease and blood clots associated with taking HRT. These risks have largely been exaggerated and the women that were included in the studies which generated these concerns were all older and had gone through the menopause naturally. They were therefore getting 'more' oestrogen than they would have had normally.

Women under the age of 50 who receive HRT after having their ovaries removed are simply 'replacing' the oestrogen that they should have had naturally. Therefore women under the age of 50 are not at increased risk.

If you are having your womb removed (hysterectomy) as well as your ovaries, then you only need to take HRT which contains oestrogen. If not, you will need to take HRT which contains oestrogen and progestogen (this is often called combined HRT). Taking oestrogen-only HRT if you have not had a hysterectomy increases your risk of developing womb (endometrial) cancer in the future.

How do I take the medication?

For the first six weeks after the operation, we recommend you have HRT in a patch form. This is to reduce the risk of you developing a blood clot in your legs or lungs after the surgery. After six weeks you can have any type of HRT you like. You can choose from tablets, patches or gels or a combination.

If you need to have progesterone (if you have not had a hysterectomy), you can have a coil containing progesterone inserted into your womb. This is called a Mirena. If you think you would like this, ask your Gynaecologist and it can be inserted during your operation whilst you are asleep. If you don't decide until later that you want to try the coil, you don't have to have an anaesthetic to have it put it – you can usually have it done at your GP surgery.

Are there any side effects?

These are common in the first few months, but women react differently to HRT, so it is sometimes a case of trying something and seeing how you get on.

- Breast pain/tenderness, bloating, nausea, headaches, leg cramps, indigestion, mood swings, acne and backache: these usually disappear after 2-3 months. If they don't, your doctor might suggest trying different type of HRT.

- Bleeding: sometimes there may be some irregular bleeding in the first few months, but this should settle. Any bleeding after 3 months will need to be investigated as it may not be from the HRT

What follow-up do I need?

We recommend that you see your GP at least every year for a check-up and when you turn 50 you might want to think about coming off the HRT but you can stay on it if you prefer. Your GP will talk to you about the pros and cons of this.

More information

You can log on to NHS choices or NICE National Institute for Health and Care Excellence on the internet, or ask your GP or Gynaecologist for more information.

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