

Should the ovaries be removed or retained at the time of hysterectomy for benign disease?

M. Hickey¹, M. Ambekar, and I. Hammond

School of Women's and Infants' Health, University of Western Australia, King Edward Memorial Hospital, 374 Bagot Road, Subiaco, WA 6008, Australia

¹Correspondence address. E-mail mhickey@meddent.uwa.edu.au

TABLE OF CONTENTS

- Introduction
- Methods
- Common indications for prophylactic oophorectomy at the time of hysterectomy
 - Reduction of the risk of ovarian cancer in women who are not at increased risk
 - Reducing the risk of ovarian cancer in women at increased risk
 - Avoidance of further gynaecological surgical interventions related to retained ovaries
 - Reduction of symptoms associated with advanced endometriosis not responsive to other medical or surgical therapies
 - Intractable and severe premenstrual syndrome
- Conclusions
- Unresolved issues requiring further research

BACKGROUND: Bilateral oophorectomy is commonly performed at the time of hysterectomy for benign disease. Indications for oophorectomy vary, but in most cases relatively little high-quality information is available to inform the surgeon or patient regarding the relative risks and benefits of ovarian conservation or removal. This review will address the common clinical situations when oophorectomy may be performed and will evaluate the evidence for risk and benefit in each of these circumstances. The aim of this review is to bring together the evidence regarding oophorectomy in pre- and post-menopausal women and to highlight the areas needing further study.

METHODS: We searched the published literature for studies related to outcomes following surgical menopause, risk-reducing surgery for ovarian cancer, surgical treatment for endometriosis, bilateral oophorectomy for benign disease and treatment for premenstrual syndrome/premenstrual dysphoric disorder.

RESULTS: Rates of oophorectomy at the time of hysterectomy for benign disease appear to be increasing. There is good evidence to support bilateral salpingo-oophorectomy (BSO) as a risk-reducing surgery for women at high risk of ovarian cancer, but relatively little evidence to support oophorectomy or BSO in other circumstances. There is growing evidence from observational studies that surgical menopause may impact negatively on future cardiovascular, psychosexual, cognitive and mental health.

CONCLUSION: Clinicians and patients should fully consider the relative risks and benefits of oophorectomy on an individual basis prior to surgery.

Key words: surgical menopause / bilateral salpingo-oophorectomy / ovarian cancer / endometriosis / premenstrual syndrome

Introduction

Despite new developments in the treatment of menstrual disorders, hysterectomy for benign disease remains a common surgical procedure. Hysterectomy rates vary greatly internationally from 55 per 10 000 in North America (<http://www.cdc.gov>) and 28 per 10 000 in Britain to 10 per 10 000 in Denmark. In addition,

hysterectomy rates vary within countries according to both patient-related factors such as race, socioeconomic and education status, private health insurance and attitudes toward surgery, as well as the training and practice of the surgeon (Wu *et al.*, 2007). In Australia, the hysterectomy rate to treat menstrual disorders has fallen, apparently in parallel with the increased availability of new treatment methods such as endometrial ablation and the levonorgestrel-releasing intrauterine device (AIHW, 2003). This has also been seen in Europe where patient preference for uterine-conserving treatments appears to be guiding practice (Bourdrez *et al.*, 2004; van Dongen *et al.*, 2009).

At the time of hysterectomy the ovaries can either be removed or retained. Oophorectomy does not add significantly to the duration or immediate complications of hysterectomy, but may have significant implications for both short- and long-term health. Surgical data are not available for all developed countries, but in the USA, the percentage of hysterectomies accompanied by bilateral oophorectomy more than doubled from 1965 (25%) to 1999 (55%) (www.cdc.gov/mmwr). Alarmingly, around 18% of US women aged 18–44 years undergo oophorectomy at the time of hysterectomy for benign disease, and around 76% are aged 45–64 years (www.cdc.gov/mmwr). Oophorectomy is more commonly performed at the time of abdominal compared with vaginal hysterectomy, probably reflecting indications for the procedure, as well as ease of the surgical access (Davies *et al.*, 1996).

In the past, menopausal hormone therapy (HT) has been confidently offered to women with menopausal symptoms following oophorectomy, with the expectation that this may also have additional health benefits. Recent evidence demonstrating that in post-menopausal women exogenous estrogens may act quite differently from endogenous estrogens, and that long-term HT that may be associated with significant risks, which may outweigh benefits (Rossouw *et al.*, 2002), has challenged this assumption. The risk of breast cancer in the general population is age related. Long-term use of combined HT containing estrogen and progestogen appears to increase the risk of breast cancer, but this is not seen with estrogen-only HT (Anderson *et al.*, 2004). Findings, from large retrospective and case–control studies, that surgical menopause may be associated with long-term cardiovascular, psycho-sexual and cognitive dysfunction (Rivera *et al.*, 2009; Rocca *et al.*, 2009) makes it timely to evaluate the role of oophorectomy at the time of hysterectomy for benign disease. Further, it remains unclear whether HT taken following surgical menopause modifies subsequent cardiovascular or cognitive function.

Each year around one-quarter of a million women in North America undergo surgical menopause due to bilateral oophorectomy (Henderson and Sherwin, 2007). The American College of Obstetricians and Gynaecologists (ACOG) has recently changed its recommendation regarding retention or removal of normal ovaries at the time of hysterectomy from suggesting that aged 45 years should be the ‘cut off’ for oophorectomy to advice that ‘strong consideration should be made for retaining normal ovaries in premenopausal women who are not at increased genetic risk of ovarian cancer’ (<http://www.acog.org/>). However, there is a paucity of evidence from high-quality clinical trials to inform both surgeons and patients in making decisions about the relative merits of ovarian removal or conservation. A recent systematic review (Orozco *et al.*, 2008) concluded that ‘there are currently no good quality studies of

the benefits or harms of removing normal ovaries at the time of hysterectomy’.

In the light of new information about the risks and benefits of HT and potential risks of surgical menopause, this review will consider the common indications for the prophylactic removal of normal ovaries at the time of hysterectomy for benign disease in pre- and post-menopausal women, and will present the current evidence to support removal or retention.

Methods

We searched the published English language literature using search engines from PUBMED, Medline, Medscape and Ovid for studies related to outcomes following surgical menopause, risk-reducing surgery for ovarian cancer, surgical treatment for endometriosis, bilateral oophorectomy for benign disease and treatment for premenstrual syndrome (PMS)/premenstrual dysphoric disorder.

Common indications for prophylactic oophorectomy at the time of hysterectomy

Reduction of the risk of ovarian cancer in women who are not at increased risk

Reduction in the future risk of ovarian cancer is the single most common reason for normal ovaries to be removed at the time of hysterectomy, particularly in the post-menopausal women (Parker *et al.*, 2007). Cancer of the ovary is the sixth most common cause of cancer death in Australian women (<http://www.ovariancancerprogram.org.au/info/statistics.html>) and the lifetime risk of ovarian cancer in Australian women is around 1 in 77 (<http://www.ovariancancerprogram.org.au/info/statistics.html>). A combination of factors including the lack of a proven efficient early screening test and non-specific presenting symptoms means that ovarian cancer tends to be diagnosed at a more advanced stage than other gynaecological cancers, and prognosis is accordingly compromised. Five year survival from ovarian cancer in Australia is only 42% and decreases with age at diagnosis (<http://www.nhmrc.gov.au/publications/synopses/cp98syn.htm>).

Hysterectomy alone reduces the risk of ovarian cancer by around 36% compared with women with an intact uterus and ovaries and this protective effect continues for up to 15 years (Chiapparino *et al.*, 2005). Between 4 and 14% of women who develop ovarian cancer have had prior hysterectomies in which ovaries were retained (Halperin *et al.*, 2004). Tubal ligation also reduces the risk of ovarian cancer by 35–40% in case–control studies (Green *et al.*, 1997), although a recent large prospective study from China failed to support this observation (Dorjgochoo *et al.*, 2008). If tubal ligation does reduce the risk of ovarian cancer, the mechanisms of this risk reduction are not clear and may be due to reduced passage of carcinogens to the upper genital tract. Currently there is insufficient evidence to support advising tubal ligation as a risk-reducing procedure for ovarian cancer.

There is little good evidence to assist the surgeon or patient in deciding whether to remove or retain normal ovaries to reduce the risk of future ovarian cancer in low-risk women. Sometimes the decision may be left until the time of surgery with the plan to retain

the ovaries 'if they appear normal'. It is not known whether a surgeon's impression of 'normality' equates reliably to histologically confirmed ovarian pathology. Clinical experience suggests that there is likely to be a high chance of false positives. Since pelvic ultrasound is very commonly performed prior to hysterectomy in developed countries and has a high sensitivity in detecting ovarian pathology (Shwayder, 2008), it seems relatively unlikely in modern surgical practice that significant ovarian pathology will be clinically apparent for the first time at the time of hysterectomy.

Impact of bilateral oophorectomy in pre- and post-menopausal women

It is estimated that in women aged 40 or over, around 5.2% of ovarian cancers could have been prevented if prophylactic oophorectomy were performed at the time of hysterectomy for benign disease (Piver, 1996). In Australia, 20% of ovarian cancers occur in women before the age of 50 (<http://www.aihw.gov.au/>).

In premenopausal women who are not from high-risk families, the risk of ovarian cancer found incidentally at the time of hysterectomy is very low. Despite this, oophorectomy is commonly performed in premenopausal women to reduce their future risk of ovarian cancer (Parker *et al.*, 2007).

The peak presentation of ovarian cancer is during the fifth and sixth decade (<http://www.ovariancancerprogram.org.au/info/statistics.html>). The background risk of ovarian cancer in women is 20 per 100 000 at aged 50 years, rising to 33 per 100 000 at aged 60 years, and 40 per 100 000 at aged 70 years (ACN&NBCC, 2004). However, relatively little is known about the short- and long-term consequences of oophorectomy in this population. Post-menopausal ovaries continue to be active and produce estradiol (at low levels) and testosterone (Rinaudo and Strauss, 2004). Total testosterone concentrations are maintained across the menopausal transition, with a fall in sex hormone-binding globulin and hence a rise in free testosterone (Burger, 2008). Ovarian testosterone undergoes peripheral conversion to estrone, and may act independently on libido, bone health and well-being. The impact of other ovarian hormones such as inhibin is largely unknown, and it is quite possible that the ovary may produce other hormonal and metabolic substances which are not yet defined.

Vasomotor symptoms: impact of premenopausal bilateral oophorectomy. Surprisingly few studies have addressed how surgical menopause impacts on subsequent menopausal symptoms. It is widely stated that menopausal symptoms following surgical menopause may be more severe and long lasting than those seen following spontaneous ovarian failure (Bachmann, 1999), but this has not been addressed in prospective or high-quality cohort studies. In women undergoing spontaneous menopause, a recent meta-analysis suggests the duration of menopausal symptoms may commonly have been underestimated, with a median duration of vasomotor symptoms of around 8 years. Approximately 10% of women continue to experience vasomotor symptoms up to 12 years after the final menstrual period (Politi *et al.*, 2008). If menopausal symptoms are more severe and long lasting following surgical menopause, this has significant implications for the duration of treatment that may be required.

Despite a paucity of high-quality data regarding the risks and benefits of estrogen containing HT in younger menopausal women, most current international guidelines advise taking HT until the

average age of natural menopause (around 51 years) (Hickey *et al.*, 2005). Further, few studies have evaluated whether HT is effective in ameliorating symptoms following surgical menopause. Recent cross-sectional data indicate that HT following bilateral salpingo-oophorectomy (BSO) as a risk-reducing procedure in younger women with BRCA1/2 gene mutation may not be effective in managing menopausal symptoms. In a postal survey of 450 premenopausal women who carried the BRCA1/2 gene mutation, 36% of women had undergone prophylactic BSO and 64% had opted for gynaecological screening. Of the prophylactic BSO group, 47% of the women were current HT users. They reported significantly fewer vasomotor symptoms than non-users ($P < 0.05$). However, compared with premenopausal women undergoing screening, oophorectomized HT users were more likely to report vasomotor symptoms ($P < 0.01$). HT users and non-users reported comparable levels of sexual functioning. Compared with women in the screening group, oophorectomized HT users reported significantly more sexual discomfort due to vaginal dryness and dyspareunia ($P < 0.01$). The authors concluded that although HT has a positive impact on surgically induced vasomotor symptoms, it may be less effective than is often assumed. Symptom levels remain well above those of premenopausal women undergoing screening, and sexual discomfort was not alleviated by HT (Madalinska *et al.*, 2006). It is possible that the lack of effectiveness of estrogen in this context may reflect doses used or mode of administration, and prospective studies are needed.

Vasomotor symptoms: impact of post-menopausal bilateral oophorectomy. Very few studies have addressed the impact of oophorectomy on menopausal symptoms in post-menopausal women. It has largely been assumed that post-menopausal oophorectomy will not induce new menopausal symptoms. However, continued endocrine production after menopause could potentially lead to symptomatic changes.

Cardiovascular health: impact of premenopausal bilateral oophorectomy. Cardiovascular disease (CVD) and particularly coronary heart disease (CHD) is a leading cause of death in older women, and the rate increases following menopause (Lobo, 2007). The reasons for this are not fully known, but may relate to an accelerated rise in cholesterol levels, blood pressure and insulin, which primarily relate to increased body weight following the menopause transition (Kannel *et al.*, 1976).

Although studies are inconsistent, a recent meta-analysis suggests that earlier spontaneous menopause is associated with an increased risk of CVD [relative risk (RR): 1.25, 95% confidence interval (CI): 1.15–1.35] (Atsma *et al.*, 2006) (Fig. 1). After controlling for age and smoking, the pooled effect was found to be 1.38 (95% CI: 1.21–1.58). The mechanism for this increase in CVD risk appears to be accelerated atherosclerosis (Lobo, 2007). It remains unclear whether HT modifies this process or the clinical CVD risk. A large randomized controlled trial failed to show any impact of unopposed conjugated equine estrogen on CVD in older post-menopausal women (Anderson *et al.*, 2004). It is not known whether different types or delivery of estrogen (and progestogen) may have 'better' cardiovascular effects, or whether a 'critical window' of estrogen exposure exists in the early post-menopausal period (Harman *et al.*, 2005). Until these data are available it appears that retention of ovarian function with endogenous estrogen may be the best way to reduce risk of CHD.

Data from large randomized controlled trials suggest that surgical compared with natural menopause may substantially increase the

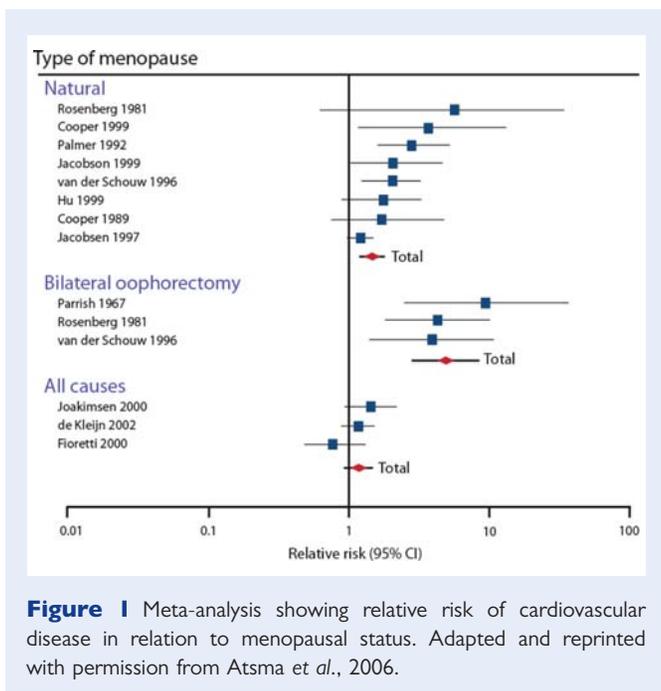


Figure 1 Meta-analysis showing relative risk of cardiovascular disease in relation to menopausal status. Adapted and reprinted with permission from Atsma et al., 2006.

risk of CVD. In the Women's Health Initiative (WHI) study, oophorectomy and hysterectomy were associated with a 2-fold increased risk of coronary artery calcification compared with those whose ovaries were retained (Allison et al., 2008). This was partially ameliorated when estrogen was used. A recent meta-analysis demonstrated that natural menopause did not increase the risk of CVD (RR: 1.14, 95% CI: 0.86–1.51) but oophorectomy, even at a mean age of 50 years appeared to increase the risk (RR: 2.62, 95% CI: 2.05–3.35) and oophorectomy at younger than 50 years had a substantial negative impact on CVD (RR: 4.45, 95% CI: 2.56–8.10) (Atsma et al., 2006). This is consistent with findings from a recent Danish cohort study where rates of ischemic heart disease were 7-fold higher in women with a history of oophorectomy younger than 45 years (Løkkegaard et al., 2006). Further, the risk of CVD, particularly CHD with early surgical menopause appears to increase with younger age at oophorectomy. The mechanism underlying this is unknown, but may relate to the action of endogenous estrogen on the endothelium. Recent prospective observational data from nearly 30 000 women in the Nurses' Health Study on long-term (24 years) health outcomes and mortality after oophorectomy or ovarian conservation at hysterectomy for benign disease showed that oophorectomy was associated with an increase in total mortality: multivariable hazard ratios (HR) of 1.12 (95% CI: 1.03–1.21); fatal plus non-fatal CHD, HR of 1.17 (95% CI: 1.02–1.35) and stroke, HR of 1.14 (95% CI: 0.98–1.33) (Parker et al., 2009). Although the risks of breast (HR: 0.75, 95% CI: 0.68–0.84), ovarian (HR: 0.04, 95% CI: 0.01–0.09, number needed to treat = 220) and total cancers (HR: 0.90, 95% CI: 0.84–0.96) decreased after oophorectomy, lung cancer incidence (HR: 1.26, 95% CI: 1.02–1.56, number needed to harm = 190) and total cancer mortality (HR: 1.17, 95% CI: 1.04–1.32) increased. For those never having used estrogen therapy, bilateral oophorectomy before 50 years of age was associated with an increased risk of all-cause mortality, CHD and stroke. With an approximate 35-year life

span after surgery, one additional death would be expected for every nine oophorectomies performed. In no analysis or age group was oophorectomy associated with increased survival.

Surgical menopause also appears to increase the risk of the metabolic syndrome. In 326 premenopausal women undergoing BSO to reduce their risk of ovarian cancer, the odds ratio (OR) of metabolic syndrome was 2.46 (95% CI: 1.63–3.73) and OR of diabetes was 2.49 (95% CI: 1.60–3.88) at a mean of 6 years postoperative follow-up (Michelsen et al., 2009).

Cardiovascular health: impact of post-menopausal bilateral oophorectomy. A recent meta-analysis of pooled data from 18 observational studies of post-menopausal status and CVD concluded that oophorectomy in post-menopausal women adversely affected the incidence of CVD (RR: 2.62, 95% CI: 2.05–3.35) compared with natural menopause (RR: 1.14, 95% CI: 0.86–1.51) (Atsma et al., 2006). Statistical modelling has linked prophylactic bilateral oophorectomy before the age of 65 years with an increase in overall mortality and CHD mortality (Shoupe et al., 2007). However, findings from the WHI Observational Study suggested that women who undergo hysterectomy (with or without oophorectomy) have worse cardiovascular risk factors at baseline with a higher proportion of hypertension, diabetes, high cholesterol, obesity and lower education, income and physical activity (all $P < 0.01$) compared with those who did not have a hysterectomy (Howard et al., 2005). Prospective data are needed to determine whether post-menopausal oophorectomy impacts on the risk of CVD.

There is some evidence that supplemental estrogen may mitigate the adverse cardiovascular effects of oophorectomy in post-menopausal women. Data from a large, prospective randomized controlled trial, the WHI Coronary Artery Calcium Study showed an increased risk of subclinical coronary artery disease in post-menopausal women who underwent both hysterectomy and bilateral oophorectomy and were not treated with estrogen compared with women who underwent hysterectomy alone (Allison et al., 2008). In those with no previous HT use, those with bilateral oophorectomy had an OR of 2.0 (95% CI: 1.2–3.4) for any coronary artery calcification (CAC) compared with women with no history of oophorectomy, whereas among women with unilateral or partial oophorectomy, the odds of any CAC was 1.7 (95% CI: 1.0–2.8). Among women with bilateral oophorectomy, HT use within 5 years of oophorectomy was associated with a lower prevalence of CAC. The authors concluded that in women with previous hysterectomy, subclinical coronary artery disease was more prevalent among those with oophorectomy and no prior HT use, independent of traditional CVD risk factors. The results suggest that factors related to oophorectomy and the absence of estrogen treatment in oophorectomized women may be related to CHD.

Cognitive function and mental health: impact of premenopausal bilateral oophorectomy. Concerns about cognitive function, particularly memory, are common during the menopause transition, but relatively little is known about the cognitive consequences of surgical menopause. A recent systematic review concluded that whilst smaller prospective studies have found that surgical menopause is associated with specific deficits in the memory (visual and verbal) and verbal fluency domains, limited data from randomized controlled trials have generally found no effect of surgical menopause on cognitive functioning (Vearncombe and Pachana, 2009).

However, a recent retrospective cohort study of 666 women who had undergone surgical menopause for benign indications age matched with women with ovarian preservation (Rocca *et al.*, 2007), suggest that oophorectomy may increase the risk of later cognitive dysfunction including dementia, depression and anxiety. The findings remained consistent after excluding depressive or anxiety symptoms that first occurred within 10 years after oophorectomy. The associations were greater with younger age at oophorectomy but did not vary across indications for surgery. Importantly, estrogen replacement in women less than 50 years at the time of surgery did not modify these risks. However, there are limitations to this study including retrospective design and failure to differentiate between uni- and bilateral oophorectomy.

Cognitive function and mental health: impact of post-menopausal bilateral oophorectomy. Observational studies of long-term mental health and cognitive outcomes of oophorectomy have largely failed to differentiate between oophorectomy performed in pre- and post-menopausal women. Hence, little is known about the impact of oophorectomy in post-menopausal on cognitive function and mental health.

Osteoporosis and fracture risk: impact of premenopausal bilateral oophorectomy. It is well established that bone loss accelerates following menopause. There is a linear relationship between earlier age at menopause and lower bone density in later life (Gallagher, 2007). Premature menopause is a well-established risk factor for osteoporosis. A recent large cross-sectional study suggested that women with early menopause (under 45 years) had a significantly lower vertebral bone mass than those with normal age or later menopause (Francucci *et al.*, 2008). The risks of osteoporosis and fracture can be reduced by taking HT in women with premature or early menopause (Gallagher, 2007), but the uptake of HT in this population is not known.

Osteoporosis and fracture risk: impact of post-menopausal bilateral oophorectomy. Observational studies suggest that retaining the ovaries in post-menopausal women reduces the risk of osteoporotic fracture (Parker *et al.*, 2007). The impact of post-menopausal oophorectomy on subsequent bone density and fracture risk is controversial. Some observational studies have shown a modest increase in risk (RR: 1.54, 95% CI: 1.29–1.82) (Melton *et al.*, 2003), perhaps due to ongoing ovarian androgen production from the post-menopausal ovary, which is peripherally converted to estrogens. Other observational studies have failed to show any impact of post-menopausal oophorectomy on subsequent fracture risk (Antoniucci *et al.*, 2005).

Quality of life and sexual function: impact of premenopausal bilateral oophorectomy. The evaluation of quality of life, well-being and sexual function following surgical menopause is complex, and will partly depend on preoperative characteristics, the indications for hysterectomy and oophorectomy and the specific procedure performed. Overall, data from high-quality studies show that quality of life (Garry *et al.*, 2004), psychological well-being and sexual function improve after hysterectomy for benign disease (Rhodes *et al.*, 1999; Shifren and Avis, 2007). However, there are limited data indicating how oophorectomy impacts on these quality of life outcomes.

Removal of the ovaries generally results in around 50% reduction in circulating testosterone levels (Davis *et al.*, 2005). Circulating testosterone levels appear to contribute to sexual desire in women. Prospective studies suggest that retaining the ovaries at the time of hysterectomy is associated with improved libido and superior sexual

function compared with those who undergo oophorectomy (Shifren and Avis, 2007). These studies may be confounded by differences in preoperative sexual function between women who chose to retain or lose their ovaries (Aziz *et al.*, 2005). A recent systematic review of hysterectomy versus hysterectomy plus oophorectomy in premenopausal women identified only two controlled studies that both addressed psychological and sexual outcomes. The authors concluded that both trials showed very low-quality evidence of a positive effect on psychological well-being for both hysterectomy and hysterectomy plus oophorectomy in premenopausal women at 1 year follow-up (Orozco *et al.*, 2008).

A recent prospective study comparing health-related quality of life (QOL) and sexual function in women undergoing hysterectomy with and without oophorectomy, for benign disease found that by 2 years there were no differences in QOL or sexual function between the groups (Teplin *et al.*, 2007). There are relatively few prospective studies of surgical menopause on these outcomes, but one prospective study of young women (≤ 46 years) found that women undergoing oophorectomy had higher depression scores before and after surgery and were more likely to have pre-existing pelvic pain (Farquhar *et al.*, 2006). Eighteen per cent of women who underwent hysterectomy with oophorectomy had pelvic pain prior to hysterectomy, compared with only 6% of those whose ovaries were conserved. This highlights a major limitation of observational studies since women choosing to undergo oophorectomy may differ from those choosing to retain their ovaries. Further, findings may be confounded depending on whether women take estrogen and/or testosterone following surgical menopause. A recent systematic review concluded that adding testosterone to estrogen therapy may provide additional improvements in well-being in some women, but only at supraphysiological levels of total testosterone and physiological levels of free testosterone (Kotz *et al.*, 2006). The current Endocrine Society clinical guidelines advise against making a diagnosis of androgen insufficiency in general, but identify surgically menopausal women as being a group likely to benefit from testosterone supplementation, at least in the short term (Wierman *et al.*, 2006). Recent evidence suggests that testosterone may still be effective in improving sexual function without the addition of estrogen (Davis *et al.*, 2008). However, the safety of testosterone alone or in combination with estrogen is not established.

Quality of life and sexual function: impact of post-menopausal bilateral oophorectomy. Most studies suggest that increasing age and post-menopausal status impact negatively on sexual function (Dennerstein *et al.*, 2001). Relatively little is known about how oophorectomy in post-menopausal women impacts on QOL or sexual function. Only one published prospective study (in Turkish women) undergoing hysterectomy and oophorectomy has measured sexual function before and after surgery in post-menopausal women using a validated measurement tool. The authors report that hysterectomy plus oophorectomy had an adverse effect on objectively measured sexual function in post-menopausal women. Sexual function was measured using the female sexual function index, and scores decreased significantly in the first 6 months following hysterectomy ($P < 0.05$) indicating a reduction in sexual function. Overall, post-operative estrogen replacement did not improve sexual function in post-menopausal women (Celik *et al.*, 2008).

Evaluating the risk–benefit ratio of prophylactic bilateral oophorectomy in post-menopausal women. A recent modelling study in women not at

increased risk of ovarian cancer concluded that the disadvantages of prophylactic oophorectomy outweigh the advantages up to the age of 65 years and concluded that 'women younger than 65 years of age clearly benefit from ovarian conservation, and at no age is there a clear benefit from prophylactic oophorectomy' (Parker et al., 2007). Over all, women undergoing oophorectomy before 55 had about 8.5% excess mortality compared with ovarian conservation. Women with oophorectomy before 59 had 4% excess mortality. The estimated benefits of ovarian conservation were largely derived from the calculated benefits of endogenous estrogen on CHD and osteoporotic fracture, an area that remains highly controversial and may rely on the timing of estrogen replacement following menopause (Harman et al., 2005).

Reducing the risk of ovarian cancer in women at increased risk

Family history may confer a significant increased risk of epithelial ovarian cancer (ACN&NBCC, 2004). When family history of ovarian and/or breast and bowel cancer suggests a significant risk of carrying a genetic mutation, patients should be referred to a Clinical Genetic Service for assessment and confirmation of their risk status and discussion of screening for specific gene mutations. Management of women known to be gene mutations carriers includes counselling, surveillance and consideration of risk-reducing surgery including prophylactic mastectomy, hysterectomy and/or BSO depending on the gene mutation identified. Advances in diagnostic genetic techniques mean that increasing numbers of women are being identified as being at increased risk for ovarian cancer due to gene mutations. Two types of ovarian cancer susceptibility genes have been identified: the BRCA1 and 2 and the mismatch repair genes associated with HNPCC. Carriers of germ-line mutations in the BRCA1 gene carry a lifetime risk ovarian cancer of 36–46% and 10–27% in those carrying the BRCA2 gene mutation (Rebbeck et al., 2009). The HNPCC mutation confers 9–12% increased risk of ovarian cancer and an increased risk for endometrial cancer up to 40% (Schmeler and Lu, 2008).

Up to 10% of epithelial ovarian cancers are thought to arise due to the inheritance of mutations in ovarian cancer-related genes (Stratton et al., 1997). Removal of normal fallopian tubes and ovaries in a woman who carries the BRCA1 or 2 gene mutation will reduce her ovarian cancer risk by 80% (Finch et al., 2006) and her breast cancer risk by 50% (Rebbeck et al., 2005, 2009). Risk reduction following BSO may differ for BRCA1/2 carriers. Case-control studies suggest that prophylactic salpingo-oophorectomy may result in a greater reduction in breast cancer risk in BRCA1 carriers who undergo surgery before 40 years of age, compared with BRCA2 carriers (Eisen et al., 2005). In 1439 patients with breast cancer and 1866 matched controls derived from a registry of BRCA1 and 2 carriers the authors estimated ORs of breast cancer for having had a bilateral oophorectomy, using conditional logistic regression, matched for parity and for oral contraceptive use. They found that a previous history of oophorectomy was associated with a significant reduction in breast cancer risk of 56% for BRCA1 carriers (OR: 0.44; 95% CI: 0.29–0.66) and of 46% for BRCA2 carriers (OR: 0.57; 95% CI: 0.28–1.15). The risk reduction was greater if the oophorectomy was performed before age 40 (OR: 0.36; 95% CI: 0.20–0.64 for

BRCA1 carriers) than after age 40 (OR: 0.53; 95% CI: 0.30–0.91). The protective effect was evident for 15 years post-oophorectomy (OR: 0.39; 95% CI: 0.26–0.57). The authors concluded that oophorectomy is an effective means of reducing the risk of breast cancer in carriers of BRCA1 mutations. Their data suggested that oophorectomy was also protective against breast cancer in BRCA2 carriers but this requires confirmation in larger studies (Eisen et al., 2005).

Both ovaries and fallopian tubes should be removed since both are at increased risk for malignant transformation (Levine et al., 2003). There is some evidence that most BRCA-related 'ovarian cancers' actually arise in the fimbrial end of the fallopian tube. This may explain why transvaginal ultrasound is not an effective screening modality in this population (Callahan et al., 2007).

Annual screening for ovarian cancer in BRCA1/2 gene mutation carriers using transvaginal ultrasound, CA125 or other markers is ineffective in detecting tumours at a sufficiently early stage to substantially influence survival in BRCA1/2 carriers, and cannot be recommended (Evans et al., 2008). The only intervention that has been shown to be effective in reducing the incidence of ovarian cancer in women carrying the BRCA1 and 2 gene mutations is BSO (Kauff et al., 2008).

Currently the decision to undergo risk-reducing BSO is likely to depend on the woman's age, personal history of cancer, known carriage of a germline mutation and fertility wishes. Of concern is the safe and effective management of menopausal symptoms and potential long-term risk of BSO in premenopausal women following risk-reducing BSO. Estrogen-containing HT is highly effective in symptomatic peri- and post-menopausal women (MacLennan et al., 2004), but there is relatively little information about the efficacy of HT in young women following surgical menopause. In a recent survey women reported limited efficacy for HT in reducing menopausal symptoms following risk-reducing BSO (Madalinska et al., 2006). Further, gene mutations that confer an increased risk of ovarian cancer commonly also increase breast cancer risk and the safety of exogenous estrogen in these women is poorly understood. Recent case-controlled (Kotsopoulos et al., 2006; Eisen et al., 2008) and retrospective (Rebbeck et al., 2005) studies are reassuring that HT does not increase the risk of breast cancer in BRCA1/2 carriers. In BRCA1 carriers (Eisen et al., 2008) estrogen-only HT conferred a small but statistically significant reduction in breast cancer risk (OR: 0.51; 95% CI: 0.27–0.98; $P = 0.04$), consistent with that seen in the larger population (Anderson et al., 2004). No statistically significant differences in breast cancer risk were seen in users of combined HT. For those women at high risk of breast and ovarian cancer who opt to undergo risk-reducing surgery, the risks and benefits of removing the uterus in addition to the ovaries are not well defined. The data from this study would support offering both hysterectomy and BSO at the time of risk-reducing surgery for BRCA1 carriers who have completed their families (Fig. 2).

For BRCA1/2 carriers who have a personal history of breast cancer, neither HT nor tibolone can be recommended (Hickey et al., 2008). In breast cancer patients, data from a prospective randomized controlled trial that did not meet its recruitment targets (the HABITS trial, hormonal replacement therapy after breast cancer, Is it safe?) at a median follow-up of 2.1 years showed that the risk for recurrence of breast cancer among patients receiving

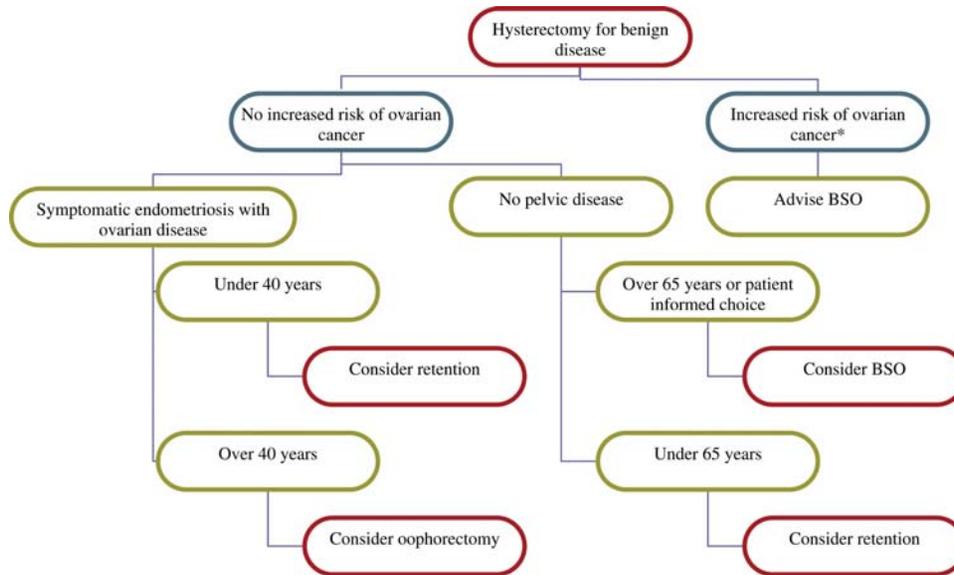


Figure 2 Proposed flow diagram to guide clinical decision-making regarding bilateral oophorectomy (BSO) at the time of hysterectomy for benign disease. *BRCA1/2 or HNPCC gene mutation or strong family history.

menopausal HT was statistically significantly higher [relative hazard (RH): 3.3, 95% CI: 1.5–7.4] compared with those receiving no treatment (Holmberg and Anderson, 2004). A parallel study of similar size (the Stockholm Trial) failed to show any effect on breast cancer recurrence in HT users at a median follow-up of 4.1 years (RH 0.82, 95% CI: 0.35–1.9) (von Schoultz and Rutqvist, 2005). The reasons for these differences in outcome are unclear, but may relate to the greater proportion of subjects taking combined HT in the HABITS study compared with the Stockholm study. Regardless, most international guidelines now advise against the use of HT following breast cancer (Hickey *et al.*, 2005). Similarly, following the breast cancer level one data has reported that use of tibolone was associated with an increased risk of breast cancer recurrence (HR: 1.40, 95% CI: 1.14–1.70; $P = 0.001$) compared with placebo at a mean follow-up of 2 years (Kenemans *et al.*, 2009).

The use of a decision aid (Schwartz *et al.*, 2009) may assist patients in weighing up the RR and benefits of risk-reducing BSO on an individual basis.

Case-control studies suggest that family history in the absence of a confirmed gene mutation may also confer an increased risk of ovarian cancer. Having a first degree relative with ovarian cancer conferred a 7-fold increased risk (OR: 7.0; 95% CI: 3.1–16). This OR was 23 (95% CI: 2.6–212) when the relative was diagnosed with ovarian cancer at under 50 years, based on 10 cases and 1 control only. In this study, the risk of ovarian cancer was also increased in women with a family history of cancer of the stomach (OR: 1.5; 95% CI: 1.0–2.1), intestine (OR: 1.7; 95% CI: 1.2–2.4), lung (OR: 1.3; 95% CI: 1.0–1.8), breast (OR: 2.3; 95% CI: 1.7–3.1), lymphomas (OR: 2.3; 95% CI: 1.0–5.1) and all sites (OR: 1.6; 95% CI: 1.4–1.9) (Negri *et al.*, 2003). A family history of ovarian cancer is likely to influence the patient and her surgeon regarding removal or retention of ovaries at the time of hysterectomy.

Avoidance of further gynaecological surgical interventions related to retained ovaries

Prophylactic removal of healthy ovaries at the time of hysterectomy for benign conditions may be performed to avoid the potential development of subsequent benign ovarian pathology such as cysts, hydrosalpinx or entrapment/adhesions, which may be symptomatic and require surgical intervention. Although ovarian cysts visible on ultrasound are relatively common following hysterectomy, affecting up to 50% (Zalel *et al.*, 1997), relatively few women (estimated at 2.75–5%) require subsequent surgery for adnexal pathology (Plöckinger and Kölbl, 1994; Holub *et al.*, 2000). Retrospective studies suggest that the risk of further surgery is greater in those who have abdominal (6%) compared with vaginal hysterectomy (<1%) with ovarian retention (Holub *et al.*, 2000). This is likely to reflect the original indication for surgery rather than the procedure itself. Recent ACOG guidelines advise that women with endometriosis, pelvic inflammatory disease and chronic pelvic pain are at higher risk of reoperation; therefore, the risk of subsequent ovarian surgery if the ovaries are retained should be weighed against the benefit of ovarian retention in these patients (www.guideline.gov/summary/summary.aspx?doc_id=12190&nbr=6287&ss=6&xl=999).

Reduction of symptoms associated with advanced endometriosis not responsive to other medical or surgical therapies

Removal or suppression of endogenous estrogen production may be an effective treatment for symptoms of endometriosis in premenopausal women. Surgical management of advanced endometriosis may include conservative surgery (restricted to local excision of disease) or hysterectomy with or without oophorectomy. However, the role

of oophorectomy in the management of advanced endometriosis is poorly defined and no randomized controlled trials have addressed this issue. A large ($n = 8000$) retrospective Canadian study showed that initial conservative surgery for endometriosis was associated with a higher requirement for re-operation within the following 2–5 years (Weir et al., 2005). A retrospective study of nearly 250 women with advanced endometriosis, managed at a US specialist centre (Shakiba et al., 2008) report that the lowest rates of re-operation for symptomatic disease (under 10%) were in those who had both hysterectomy and bilateral oophorectomy as a primary procedure. When the uterus was removed but ovaries conserved, re-operation rates were 13% at 5 years and 23% at 7 years. Around half of those who had only local excision of endometriosis (with uterine and ovarian conservation) required further surgery by 7 years. The authors suggest that hysterectomy with ovarian preservation should be considered since it is associated with a lower re-operation rate than local excision alone.

When data from younger women (under 40 years) with advanced disease were analysed separately, this retrospective study showed that time to repeat surgery did not differ depending on whether the ovaries were removed or retained at the primary procedure. Since oophorectomy is associated with other significant disadvantages in terms of earlier menopause, the authors suggest that hysterectomy with ovarian conservation should be considered for advanced endometriosis women aged under 40 years (Shakiba et al., 2008).

Relatively few studies have addressed the RRs and benefits in terms of re-operation rates and recurrent pain of hysterectomy with or without bilateral oophorectomy for advanced endometriosis (Vercellini et al., 2009). Overall, the data suggest that preservation of any ovarian tissue is associated with substantially higher rates of recurrent pain and need for re-operation compared with ovarian removal (Namnoum et al., 1995). Small studies of younger women with advanced disease suggest that although hysterectomy and oophorectomy are effective at alleviating pain, residual symptoms of estrogen deficiency may be common (MacDonald et al., 1999).

Further, there is no consensus about how menopausal symptoms should be managed following oophorectomy for endometriosis. Estrogen-only HT has been associated with disease recurrence and uncommonly with endometrioid adenocarcinoma following oophorectomy for endometriosis (Areia et al., 2004). This has led to recommendations to use tibolone or combined estrogen and progestogen, following oophorectomy and hysterectomy for endometriosis, in an attempt to prevent estrogenic proliferation (Soliman and Hillard, 2006); however, there is no evidence to support these regimens being less likely to lead to endometrioid adenocarcinoma. Further, there is now good evidence that long-term combined HT may increase the risk of post-menopausal breast cancer that exceeds that of estrogen alone, at least in older populations (Rossouw et al., 2002). This should be considered before recommending combined HT following hysterectomy and might outweigh theoretical benefits in terms of reduced risk of endometrioid adenocarcinoma with combined HT. Combined HT and tibolone have also been linked with recurrent endometriosis (Sundar et al., 2007). The use of HT after bilateral oophorectomy for endometriosis remains controversial and requires careful counselling about possible recurrence and close follow-up.

Intractable and severe premenstrual syndrome

PMS affects up to 95% of women, of which around 5% experience severe symptoms including behavioural, psychiatric and physical symptoms (Di Giulio and Reissing, 2006). One retrospective study of a highly selected population of British women with severe PMS suggests that abdominal hysterectomy and bilateral oophorectomy may be an effective treatment (Cronje et al., 2004). The authors report that 96% of their patients were 'satisfied' or 'highly satisfied' with their treatment. Several women had not tried any other established treatment for severe PMS. Nearly all subsequently took high-dose estrogen and testosterone (as implants) and around 25% were younger than 40 years at the time of surgery. Abdominal hysterectomy was performed concurrently because of 'progesterone intolerance' or other gynaecological pathology. It is unclear why all hysterectomies were performed via the abdominal route. The authors suggest 'tripling' the effects of oophorectomy using GnRH agonists prior to surgery in these patients, although there is no evidence that this represents a realistic trial of the impact of surgical menopause and was not done in their study.

Conclusions

The decision to remove healthy ovaries in women of any age at the time of hysterectomy for benign disease should only be made following adequate and individualized counselling of the RRs and benefits of conservation or removal. In premenopausal women there are likely to be significant implications in terms of symptoms and short- and long-term risk factors for morbidity and mortality. In post-menopausal women the risks are less well defined, perhaps due to a paucity of research in this area. In women of all ages, it remains largely unclear whether estrogen replacement reduces or eliminates these risks. Mathematical modelling of risks and benefits of oophorectomy suggests that for women at low risk of ovarian cancer, ovarian conservation until at least age 65 seems to benefit long-term survival (Parker et al., 2007). Preoperative counselling should include discussion of individualized risks and benefits of ovarian removal or conservation, including the potential impact on long-term risks of breast and ovarian cancers, coronary artery disease, osteoporosis, depression and the likely efficacy and safety of HT. A decision aid may be helpful (Pell et al., 2002).

In younger women with advanced endometriosis hysterectomy with ovarian conservation should be considered. In those with severe PMS there is insufficient evidence to recommend oophorectomy as a safe and effective treatment strategy. Larger prospective studies are needed in to define the risks and benefits of oophorectomy at the time of hysterectomy.

Unresolved issues requiring further research

The nature and severity of menopausal symptoms and their impact on quality of life following surgical menopause needs to be addressed in adequately powered prospective studies. Further, relatively little is known about the uptake and efficacy of HT in this population. More information is needed about the long-term impact of BSO on CVD, cognitive function, psychosexual function, osteoporosis and quality

of life. The normal physiology of the post-menopausal ovary has not been extensively studied, and it is possible that removal of the post-menopausal ovaries may have greater consequences than has previously been believed. It is clear that the effects of bilateral oophorectomy in pre- and post-menopausal women at the time of hysterectomy are a fertile ground for clinically significant research.

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