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Review

Hormone replacement therapy in gynecologic cancer survivors: Why not?

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ABSTRACT

Purpose. As a result of treatment, many women with gynecologic malignancies will go through menopause and display climacteric symptoms at an earlier age than occurs naturally. Iatrogenic menopause may adversely affect quality of life and health outcomes in young female cancer survivors. Hormone replacement therapy (HRT) has often been withheld from women with gynecologic cancer because of concern that it might increase the risk of relapse or the development of new primary cancers. The purpose of this review was to examine the published literature on menopause management in gynecologic cancer survivors and highlight the risks and benefits of conventional and alternative HRT in this population.

Methods. A comprehensive literature search of English language studies on menopause management in gynecologic cancer survivors and women with a hereditary predisposition to a gynecologic malignancy was performed in MEDLINE databases through December 2010.

Results. Both our review and a 2008 Cochrane review of randomized trials on the effects of long-term HRT demonstrate that for menopausal women in their 40s or 50s with and without gynecologic cancer, the absolute risks of estrogen-only HRT are low. Several prospective observational studies and randomized trials on HRT use in women with a genetic predisposition for or development of a gynecologic malignancy suggest benefits in quality of life with no proven adverse oncologic effects as a result of short-term HRT use.

Conclusion. In select women, it is reasonable to discuss and offer conventional HRT for the amelioration of menopausal symptoms and to improve quality of life. HRT does not appear to increase the risk of gynecologic cancer recurrences; however, this conclusion was largely based on observational data and smaller prospective studies.

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Introduction

Over 75,000 U.S. women will be diagnosed with a gynecologic malignancy in 2011 [1]. As survival rates have improved due to advances in earlier detection and cancer treatment, quality of life has emerged as an important care component for women with gynecologic cancers. Approximately 30–40% of all women with a gynecologic malignancy will be diagnosed while pre- or peri-menopausal [1,2]. Following surgery, chemotherapy and/or radiation, many of these women will experience climacteric symptoms and menopause at an earlier age than occurs naturally. Therefore, the search for effective and safe hormone replacement therapy (HRT) is of particular interest.

The publication of the Women's Health Initiative (WHI) study in 2002 raised concerns about the risk of breast cancer, venous thromboembolic disease and other conditions associated with long-term HRT use [3]. Consequently, the pendulum swung from wholesale endorsement of extended HRT for the prevention of heart disease, osteoporosis, and improvement of menopausal symptoms, to a mass discontinuation of hormone therapy. However, follow-up studies from WHI show that many of these risks disappear after discontinuation of HRT, and in younger women who use short courses of HRT the absolute risks are quite low. In women unaffected with cancer, the current recommendation is the use of HRT in the smallest effective dose with frequent reassessment, after discussion of risk/benefit ratio.

Compared to women without cancer, HRT is less frequently prescribed in gynecologic cancer survivors due to the theoretical risk of stimulation of quiescent residual malignant cells [3]. The question remains whether HRT is truly contraindicated in these patients. Clinical decision making has been limited by the lack of large clinical trials, and in the aftermath of the WHI study, future large HRT trials are unlikely to be undertaken. Nevertheless, data does exist that may help clinicians and cancer patients make informed decisions regarding utilization of HRT in select women with reproductive malignancies. This review article aimed to summarize the existing literature on the effectiveness and safety of hormone replacement therapy in gynecologic cancer survivors and women predisposed to hereditary reproductive cancer syndromes. Hormonal, conventional non-hormonal and alternative therapies were also comprehensively reviewed.

Menopause and anti-cancer therapies

Menopause, defined retrospectively as the complete cessation of menses for at least twelve months, occurs at a mean age of 51 years among U.S. women. The menopausal state is characterized by a significant drop in the number of oocytes due to follicular atresia, leading to the decline and eventual cessation of ovarian estrogen and progesterone production [4].

Consequences of menopause include both short-term and long-term adverse effects on health and quality of life. The most prominent menopausal symptoms are summarized in Table 1 [5]. The onset of iatrogenic menopause after treatment for gynecologic cancer is usually more sudden and severe than with physiologic menopause, and many patients experience problems with adjustment. Moreover, the stress of a cancer diagnosis may exacerbate the severity of menopausal symptoms [6].

Menopause in younger women with gynecologic malignancies most often occurs due to complete surgical extirpation of ovarian tissue, resulting in an abrupt physiologic state of estrogen deprivation. Recent prospective observational data from the Nurse's Health Study further suggests that premenopausal excision of bilateral ovaries may significantly increase a woman's lifetime risk of heart disease and all-cause mortality [7]. An important exception, however, is in women at high risk for the development of ovarian or breast cancers, in whom all-cause mortality is decreased after risk-reducing bilateral salpingo-oophorectomy [8].

Even among young cancer survivors whose ovaries are completely or partially preserved at surgery, ovarian function may be compromised by chemotherapy and radiation treatment. The majority of cytoxic chemotherapy drugs affect actively dividing cells, and lead to dysmaturation of oocytes [9]. Studies of childhood patients treated for lymphoma have shown <10% rate of ovarian failure following the use of cyclophosphamide and procarbazine. There is tremendous variability in the time to recovery of ovarian function and return of menses following chemotherapy, with older age, concomitant radiation exposure, and use of alkylating agents (especially cyclophosphamide and cisplatin) being significant risk factors for ovarian failure [10,11].

Radiation appears to be even more toxic to the ovaries than chemotherapy, with dose-dependent effects. Studies on infertility suggest that a 2 Gray (Gy) radiation dose to the ovaries will produce lethal damage in half of the oocyte populations (LD 50) and that doses of ≥6 Gy may cause irreversible hypogonadism [12]. Women older than 40 years appear to be more susceptible to the effects of radiation, as evidenced by amenorrhea and raised gonadotrophin hormone levels in treated patients [13].

Benefits and risks of HRT

Multiple observational and randomized controlled trials have demonstrated that in symptomatic women, both combination and estrogen-only HRT result in significant improvement in vasomotor symptoms (hot flashes), vaginal dryness, mood and overall mental health, sleep, bone health and quality of life when compared to placebo or alternative treatments [14–18]. One recent randomized study also demonstrated a significant reduction in incidence of

Table 1
Common menopausal symptoms experienced by U.S. women.

Clinical symptom	Description
Vasomotor symptoms	• Occurs in 75% of menopausal women. • Unknown pathophysiology but may result from dysfunctional thermoregulation and inappropriate peripheral vasodilatation. • Timing: May occur several times daily and disrupt sleep cycle. Usually cease within 5 years, but minority of women experience symptoms >70 years. • Exacerbated by smoking.
Vaginal dryness	• Noted in up to 41% of women but is likely under-reported due to embarrassment, cultural reasons. • Due to de-estrogenation. Contributes to general vulvovaginal atrophy, and associated with reduced vaginal stretch, capacity, and epithelial thickness. • Associated symptoms: apareunia, dyspareunia, genital itch, burning, bleeding or discharge. • Exacerbated by smoking.
Osteoporosis	• Characterized by reduction in bone mass and disorganization of bone micro-architecture. • Imbalance in bone metabolism favoring increased bone resorption (osteoclastic activity) relative to bone formation (osteoblastic activity). • Significantly increased risk of bone fractures (vertebral fractures being most common). • Most prominent areas of bone loss are spine, hips and wrists.
Mood disturbances	• Partly a result of withdrawal of estrogen induced increase in endogenous opioids. • Sleep disturbances also occur and are confounded by nocturnal hot flashes. • Other neurotransmitter dysfunction may be involved, such as dopamine and serotonin signalling.

colorectal cancer with combination estrogen–progestin therapy [17]. Based on a recent Cochrane review of randomized trials, HRT remains the most effective treatment for menopausal symptoms [14].

In the 1990s, results from prospective clinical trials suggested that estrogen supplementation in postmenopausal women would not only effectively treat menopausal symptoms but would also lower the incidence of cardiovascular disease [15]. However, subsequent studies demonstrated significant adverse effects of long-term HRT utilization and called into question the purported cardiovascular benefits of this therapy. Two of these landmark trials are the Heart and Estrogen/Progestin Replacement Study (HERS) trial and the Women's Health Initiative (WHI) study [15–18].

Published in 1998, the HERS trial was a double-blind, placebo-controlled trial designed to study the effect of conjugated estrogens and medroxy-progesterone acetate on the risk of cardiovascular endpoints (non-fatal myocardial infarctions and heart disease-related deaths) in 2763 postmenopausal women with established coronary heart disease [15]. However, there were no differences in any cardiovascular outcomes between the treatment and placebo groups. The follow up HERS II study [16] published in 2002 was designed to analyze any possible long-term effects of estrogen/progestin therapy on cardiovascular risk. There was no reduction in cardiovascular risk between the treatment and placebo groups (relative risk with HRT: 1.00, 95% CI 0.77–1.29). However, subgroup analyses of the HERS data demonstrated improved mood and sleep patterns with HRT.

The WHI trial [17] had four distinct randomized interventions incorporated into the study schema, including two placebo-controlled, double-armed trials designed to study the effects of HRT on several menopausal endpoints. The main outcomes were risk of coronary heart disease and invasive breast cancer. Secondary outcomes included incidence of stroke, venous thromboembolic disease (DVT), breast cancer, colorectal cancer, gallbladder disease, osteoporosis and hip fracture. The study results are summarized in Table 2. Among the 16,608 women with intact uteri in the combined hormone arm of the trial (continuous estrogen–progestin therapy), there was a significantly reduced risk of hip fracture and colorectal cancer, but surprisingly, a significantly increased risk of cardiovascular heart disease, stroke, DVT and breast cancer. One possible explanation for the increased cardiovascular risk seen with HRT was that the mean age of the study participants (61 years) was older than that observed in previous HRT trials. Post hoc analysis also revealed that excess coronary heart disease occurred only in elderly (>65 years) menopausal women.

However, in an updated 2008 Cochrane review on the effects of long-term HRT in peri and postmenopausal women (based on 19 randomized trials), there was actually no difference in mortality rates from cardiovascular disease, stroke or any cancer, in women who used HRT versus placebo [14]. Additionally, a recent WHI study update demonstrated no increased risk of cardiovascular disease, stroke or DVT 3 years after discontinuing a course of HRT [18].

Table 2
WHI study: Hazard ratios for clinical outcomes in women ages 50–79.

Outcome	Hazard ratio (95% CI) for estrogen/progestin	Hazard ratio (95% CI) for estrogen only
Stroke	1.41 (1.07–1.85)	1.39 (1.10–1.77)
Breast cancer	1.24 (1.01–1.54)	0.77 (0.59–1.11)
DVT	1.95 (1.43–2.67)	1.47 (1.06–2.06)
Coronary heart disease	1.24 (1.00–1.54)	0.95 (0.70–1.16)
Hip fracture	0.66 (0.45–0.98)	0.61 (0.41–0.91)
Colorectal cancer	0.63 (0.43–0.92)	1.08 (0.75–1.55)
Dementia	2.05 (1.21–3.48)	1.49 (0.83–2.66)
Gallbladder disease	1.59 (1.20–1.97)	1.67 (1.35–2.06)
Mortality	0.98 (0.82–1.18)	1.04 (0.88–1.22)

Abbreviations: DVT = deep venous thrombosis.

Importantly, in the WHI study arm analyzing conjugated estrogen alone versus placebo in nearly 11,000 women who had undergone hysterectomy, while the risk of stroke and DVT remained with HRT, an increased risk of heart disease and breast cancer were *not* observed [17]. In fact, the relative risk of breast cancer with estrogen replacement was 0.77 (95% CI 0.59–1.01), suggesting that the progestin component of combination HRT may be the major player which potentiates breast cancer risk observed in the combination HRT study arm (Table 2). These results of estrogen-only therapy in women post-hysterectomy are more applicable to gynecologic cancer survivors who often undergo hysterectomy ± salpingo-oophorectomy and are potential candidates for estrogen-only therapy. Notably, the 2008 Cochrane review demonstrated that the absolute risks of estrogen-only HRT in younger women aged 50–59 were quite low, suggesting that it is safe to consider in this population ([14]; Table 3).

BRCA gene mutation carriers

Several observational studies and meta-analyses have demonstrated that risk-reducing salpingo-oophorectomy (RRSO) significantly reduces the risk of ovarian, fallopian tube and breast cancers in BRCA gene mutation carriers and improves overall survival [8,19–21]. Most carriers are premenopausal at the time of intervention [19], and are at risk of significant deterioration in quality of life associated with abrupt surgical menopause. A recent survey study of BRCA 1/2 mutation carriers who had undergone RRSO revealed severe vasomotor symptoms and a decrease in sexual functioning in most participants [20]. BRCA mutation carriers who undergo RRSO may opt for a course of HRT post operatively, but there are concerns regarding potentiating their already increased risk of breast cancer. Notably, however, the typical prescribed doses of estrogen (±progesterone) are considerably lower than physiologic hormone levels in premenopausal women, and it would be difficult to meaningfully increase a BRCA carrier's breast cancer risk as it is already extremely elevated.

Armstrong et al. performed a decision analysis on pooled epidemiologic studies of women with BRCA1 and 2 mutations and concluded that HRT after RRSO was associated with a short-term benefit on life expectancy, up to age 50 years [21]. Further, Rebbeck et al. evaluated whether the breast cancer risk reduction conferred by RRSO in BRCA1 and 2 mutation carriers was altered by use of post-RRSO HRT [22]. In this prospective cohort study of 462 women, RRSO was significantly associated with breast cancer risk reduction (hazard ratio [HR] = 0.40; 95% CI, 0.18 to 0.92), and HRT use of any type after RRSO did not significantly alter the reduction in breast cancer risk associated with RRSO (HR = 0.37; 95% CI, 0.14 to 0.96). The authors concluded that short term HRT use does not negate the protective effect of RRSO on subsequent breast cancer risk in BRCA 1 and 2 mutation carriers.

An important consideration in BRCA mutation carriers is that the majority of breast cancers that develop are estrogen/progesterone receptor-negative [23], providing further rationale for consideration of estrogen-based HRT. In a study of 456 BRCA mutation carriers by Eisen et al., 68% of BRCA-associated breast cancers were estrogen receptor negative, and there was no increased rate of cancer in those BRCA carriers on HRT use [24]. Interestingly, HRT use was associated

Table 3
WHI study: Absolute risk of breast cancer and thromboembolic events in women ages 50–59.*

Outcome	Estrogen/progestin	Estrogen only
Breast cancer	6 (5–7)	2 (1–4)
Stroke	7 (5–10)	2 (0–4)
DVT	1 (1–2)	1 (1–2)

*Number of additional events/1000 HRT users over a 5-year period.

with a significantly *reduced* risk of breast cancer (odds ratio 0.58, 95% CI 0.35–0.96) in this study.

The risk of, or existing diagnosis of, breast cancer, as well as the decision to perform a concomitant hysterectomy at the time of RRSO, may influence the use of HRT in gene mutation carriers. A recent bulletin from the American College of Obstetrics and Gynecology states that reasons a clinician might offer concomitant hysterectomy include (1) a desire to completely excise the fallopian tubes due to a theoretic risk of fallopian tube cancer, (2) to reduce the risk of endometrial pathology in women who will be on tamoxifen therapy, and (3) simplification of HRT so that estrogen-only therapy may be considered [25]. Therefore, given the results of the WHI study suggesting that estrogen therapy alone does not adversely impact breast cancer risk, a valid rationale for performing a hysterectomy with RRSO would be to permit estrogen-only HRT if desired by either the patient or the physician.

Finally, extreme caution should be exercised in considering HRT in BRCA mutation carriers with a history of estrogen or progesterone receptor-positive breast cancers. There is evidence that combination estrogen–progestin regimens are associated with new breast cancers in women with a prior history of breast cancer. The Hormone Replacement Therapy After Breast Cancer — Is It Safe? (HABITS) trial [26] was stopped prematurely in 2003 following an unacceptably high incidence of recurrent, contralateral and metastatic disease in women with a history of treated stage II breast cancer who received hormone replacement therapy. In the setting of a previous diagnosis of hormone positive breast cancer, we recommend against using HRT.

Recommendations:

- In BRCA mutation carriers who have undergone RRSO ± hysterectomy *without* a personal history of breast cancer or other absolute contraindications to HRT use, and who experience significant menopausal symptoms, it is reasonable to offer a short course of HRT treatment (Level II evidence).
- In BRCA mutation carriers *with* a personal history of hormone-dependent breast cancer, HRT should be avoided and non-hormonal alternatives should be first-line in the treatment of menopausal symptoms (Level II evidence).

Lynch II syndrome gene mutation carriers

Lynch II syndrome, or hereditary non-polyposis colorectal cancer (HNPCC) syndrome, is caused by defects in the mismatch repair gene. In addition to possessing an increased risk of colon cancer and other gastrointestinal tumors, women with this syndrome also have a 40% to 60% lifetime risk of developing endometrial cancer and a 12% lifetime risk of ovarian cancer [27]. One in six HNPCC-related endometrial cancers is seen in women under 40 years of age [27,28]. The age of onset of gynecologic cancers in patients with Lynch associated germ-line mutations is about 2 decades earlier than that observed in sporadic cancers and prophylactic surgeries are often recommended for risk reduction. Schmeler et al. [28] demonstrated that prophylactic hysterectomy and bilateral salpingo-oophorectomy are effective in preventing endometrial and ovarian cancers in Lynch syndrome patients.

The role of hormones in cancer genesis in HNPCC mutation carriers is not yet well elucidated. For example, estrogen-induced cell proliferation can lead to upregulation of mismatch repair (MMR) pathway, which may be protective against estrogen-induced (endometrial) malignancies in Lynch syndrome patients. However, it has also been noted that estrogen may induce MMR dysregulation and microsatellite instability via mutations or methylation of key MMR pathway proteins [29].

There are no published studies regarding the safety profile of HRT use in women with Lynch II syndrome who have undergone risk-reducing gynecologic surgery. It is also not clear if there are adverse biologic interactions of estrogen/progestin therapy in patients with DNA-mismatch repair gene defects with an intact uterus. However, there is no compelling evidence to suggest that it is unsafe to consider a course of HRT in women who have undergone risk-reducing hysterectomy/BSO. In addition, from a colon cancer risk perspective, given that estrogen therapy was shown to reduce the risk of colon cancer in the WHI study, it is possible (though unproven) that estrogen replacement could also reduce the risk of colon cancer in this subgroup of women.

Recommendations:

- There are currently no published data directing HRT use among women with Lynch II syndrome.
- It is reasonable to consider a short course of HRT in symptomatic young women who have undergone risk-reducing hysterectomy and BSO with subsequent surgical menopause.

Endometrial cancer

Endometrial cancer is the most common gynecologic malignancy, with 42,000 new cases diagnosed annually in the U.S. [1]. While the majority of endometrial cancers are diagnosed postmenopausally, approximately 25% are detected in pre-menopausal women [30,31]. When considering the rising obesity epidemic in the U.S. and the association of obesity with endometrial cancer, the percentage of premenopausal women diagnosed with this malignancy may continue to grow. Most women diagnosed with early-stage disease are cured following surgical therapy. The majority of endometrial cancers are hormone-dependent, and after standard surgical treatment of this condition, a hysterectomy, BSO and lymph node assessment, many women experience debilitating menopausal symptoms. A recurring question has been whether estrogen replacement therapy can be safely administered in this cohort.

Multiple studies have supported the potential safety of HRT in endometrial cancer survivors. Creasman et al. [32] reported one of the earlier studies in 1986, on 47 patients with stage I endometrial cancer treated in a nonrandomized fashion with conjugated estrogen for a mean duration of 26 months. Compared to 174 placebo controls, the recurrence rate was significantly lower at 2% in the treatment group versus 15% among controls after follow up between 25 and 150 months. The authors concluded that estrogen therapy was not associated with an increase in recurrence or death rates, and was not contraindicated in this population of women. Similarly, two retrospective reports on women with stage I–II endometrial cancer treated with oral estrogen ± progestin therapy demonstrated no increase recurrence risk or adverse survival outcomes when compared to endometrial cancer survivors who were not treated with HRT [33,34].

The only randomized study addressing this question was conducted by the Gynecologic Oncology Group (GOG), but was closed early due to poor accrual following the publication of the WHI study in 2002. Barakat et al. [35] reported on 618 patients with a median age of 57 and with stage I–II endometrial cancer treated with estrogen for a planned duration of 3 years following primary surgery, and 618 matched placebo controls (total 1236 patients of a planned 2108 sample size). Most tumors were of endometrioid histology with <50% myometrial invasion. The compliance rate in the treatment group was 41%. After a median follow-up of 35.7 months, the recurrence rates were 2.3% and 1.9% in the treatment group and controls, respectively ($p = NS$). The respective progression-free survival rates were 94.3% and 95.6% for the treatment and placebo groups. The authors reached the limited conclusion that the relative risk of recurrence and death from estrogen therapy after treatment for early stage endometrial cancer was 1.27 (80% CI 0.92 to 1.77) but this was not significant and the risk of recurrence was exceedingly low in both groups. Notably, however, a post hoc analysis of this randomized, double blind trial revealed that African–American women who receive HRT post-cancer

treatment may have an increased risk of recurrence compared to their matched Caucasian counterparts who also receive HRT [35]. However, these results should be interpreted with caution as only 109 African–American women were included in the analysis, which was not powered to evaluate the association of HRT and clinical outcomes within the context of race.

Another strategy to prevent early menopause in select premenopausal women with apparent early-stage, low grade disease is ovarian conservation at the time of staging surgery. However, this approach needs to be considered with caution given the increased risk of dual primaries in younger women. Given that bilateral salpingo-oophorectomy subjects women to the long-term sequelae of estrogen deprivation (with possible little net benefit in cancer risk reduction women with apparent early-stage, low-grade disease), Wright et al. recently examined the safety of ovarian preservation in young women with endometrial cancer who underwent hysterectomy [2]. In this Surveillance, Epidemiology, and End Results (SEER) analysis, over 3000 endometrial cancer survivors were identified, including 402 who underwent ovarian conservation at the time of their endometrial cancer staging surgeries [2]. On multivariate analysis, ovarian preservation had no significant effect on either cancer-specific survival (hazard ratio [HR] = 0.58; 95% CI, 0.14 to 2.44) or overall survival (HR = 0.68; 95% CI, 0.34 to 1.35). The findings were unchanged when women who received pelvic radiotherapy were excluded. The authors concluded that in select young women with apparent early-stage, low grade cancers and no suspicious appearing adnexae at the time of surgery, ovarian preservation may not be associated with an increased risk in cancer mortality in select cases.

Recommendations:

- Women with low risk, early-stage endometrial cancer who have undergone a hysterectomy/BSO and staging procedure can be offered a short course of estrogen-based HRT (at the smallest possible doses) if they suffer from menopausal symptoms (Level I–III data).
- There are no data to guide the use of estrogen replacement therapy in women with Type II endometrial cancers.

Ovarian cancer

Some theories regarding ovarian carcinogenesis describe the stimulation of estrogen receptors as a potential mechanism, yet data implicating hormonal causes are sparse. Additionally, most women with epithelial ovarian cancer do not express tumoral estrogen/progesterone receptors. The WHI study group performed a post hoc analysis for gynecologic cancer risks after 5.6 years of follow-up in the combined estrogen/progestin arm [36]. A significantly increased risk of ovarian cancer was not observed (hazard ratio 1.58 (95% CI 0.77–3.24). On the other hand, the Million Women Study identified a correlation between risk of epithelial ovarian carcinoma and history of HRT in 909,946 women [37]. The incidence rates in current and never users of hormones were 0.52 and 0.40 per 1000 years, respectively. The absolute risk of ovarian cancer was low, however, with one additional case/8300 women per year observed in those on HRT. Recently, a recent meta-analysis of 15 studies on HRT use in ovarian cancer survivors did not demonstrate an association between estrogen use and ovarian cancer [36].

Approximately 40% of women diagnosed with ovarian cancer are between 30 and 60 years of age, and 60% present with advanced disease (stages III–IV). Primary aggressive surgery and chemotherapy in these patients, with the attendant impact on sexual and psychological functioning due to abrupt menopause, raise the question of whether it is safe to consider HRT use in epithelial ovarian cancer survivors. Bebar [38] reported on a small retrospective cohort of 31 ovarian cancer patients treated with primary surgery and chemotherapy and then prescribed non-conjugated estrogens for a mean duration of 25 months. Median follow-up was 55 months. Progression of disease occurred in only three patients, and one patient developed early-stage breast cancer. Eeles et al. [39] conducted another retrospective study of 373 ovarian cancer patients who had staging surgeries; 78 received various HRT formulations for a mean of 28 months and 295 did not. The treatment group had a significantly higher number of younger women, mostly between ages 30 and 40 years, with earlier stage disease and well-differentiated tumors. However, after controlling for age, disease stage, tumor grade and interval to recurrence, there was no significant difference in disease-free survival between those women who had undergone treatment with HRT and those who had not.

In one of two more recent Phase III trials, Guidozzi et al. [40] studied 130 patients diagnosed with advanced stage, high grade serous ovarian cancer. Those who had previously taken estrogen or had ovarian tumors of low malignant potential were excluded. All patients underwent cytoreductive surgery followed by cisplatin-based chemotherapy, and were randomized to receive either oral Premarin 0.625 mg daily versus placebo. Median follow up time was 4 years, and survival analysis failed to show an adverse effect of HRT on recurrences or survival.

In a subsequent study, Mascarenhas et al. [41] reported on 799 women with epithelial ovarian cancer and 649 women with borderline ovarian tumors who were assessed regarding pre and post-cancer utilization of HRT using self-administered questionnaires. In the epithelial cancer group, 26% used pre-treatment hormones, and 40% of patients had early-stage disease, were under 60 years of age, and had well to moderately-differentiated disease. The use of HRT before treatment did not increase the relative risk of death (RR = 0.69; 95% CI 0.48–0.98). Use of HRT after treatment of ovarian cancer was also not associated with an increased risk of death (RR = 0.57; 95% CI 0.42–0.78). In the borderline cancer cohort, 21% used HRT pre-cancer and 34% after treatment. There was no effect of hormone use on the 5-year survival rate (overall survival = 93%). There was the possibility of selection and age bias in this study (with older patients who had more advanced disease declining to participate), and also an element of recall bias with information regarding hormonal treatment.

Finally, the use of HRT has not been studied in women with low grade serous ovarian carcinoma. To our knowledge, however, there is no data that either supports or refutes the use of HRT in this patient cohort. A recent report by Schlumbrecht et al. on clinicodemographic factors associated with low grade serous carcinoma suggested that anti-estrogen hormone consolidation appeared to be associated with better OS (HR, 0.15; P = .06) and better PFS (HR, 0.44; P = .07) [42]. However, this was not statistically significant and prospective trials are needed to clarify this association.

Recommendations:

- Symptomatic women with epithelial ovarian cancer may be offered a course of HRT (Level I–III evidence).
- Caution should be exercised in women with estrogen/progesterone expressing tumors.

Cervical cancer

Recent reports suggest that the majority of cervical squamous cell and adenocarcinomas are not hormone dependent [3,6]. In women with early-stage squamous cell carcinoma, it is reasonable to consider ovarian conservation in the absence of obvious metastases. However, the adenocarcinomas, which represent 15–20% of cervical cancers are associated with a higher rate of ovarian metastases at the time of diagnosis (4%) [43]. While it is known that ER/PR receptors exist in the cervix, two surgicopathological studies failed to show any prognostic significance of hormone receptor expression in patients with cervical squamous cell and adenocarcinomas [44,45]. While there are no data that confirm that cervical cancers are hormone dependent, bilateral salpingo-oophorectomy may still be more likely to be performed at the time of hysterectomy in patients with adenocarcinomas because

of the risk of metastatic disease in the ovaries. In an effort to determine whether HRT was associated with an increased risk of cervical cancer, Lacey et al. [44] performed a case control study of 570 women with and without cervical cancer and found that estrogen use was not associated with an increased risk of developing squamous cell carcinoma (odds ratio 0.85; 95% CI 0.34–2.1) or with adenocarcinoma (odds ratio of 2.0; 95% CI 0.95–4.6).

There are no randomized trials evaluating estrogen therapy in women treated with either surgery or radiation for cervical cancer. Issues in patients treated with surgery relate to the abrupt menopause that occurs after ovarian extirpation in patients not deemed candidates for ovarian conservation or oophorpexy. The local effects of radiation lead to dyspareunia and sexual dysfunction from vaginal atrophy that is compounded by the concomitant lack of estrogen [46–48]. Patients whose ovaries are left in the pelvic radiation field, or those unfortunate enough to develop ovarian failure after oophorpexy from radiation scatter may suffer from severe menopausal symptoms.

Ploch [48] prospectively studied 120 menopausal women with invasive cervical cancers treated with HRT after primary surgery or radiation. Three cohorts of 40 women each who had received estrogen, estrogen/progestin, and placebo, respectively were followed for 5 years. Recurrence rates were 20% in the HRT cohort and 32% in the placebo group, and five-year survival favored the HRT group (80% versus 65%). Therefore, there are currently no data to suggest that cervical cancer is 1) hormonally related or that 2) prognosis is worsened by HRT.

Recommendations:

- HRT use in cervical cancer survivors appears safe to consider (Levels II–III).

The emergence of non-hormonal therapies

For women with moderate-to-severe hot flashes and/or other menopausal symptoms in whom estrogen therapy is contraindicated, not well tolerated or not desired, or for women who discontinue estrogen and experience recurrent symptoms, several promising non-hormonal prescription therapies have emerged as alternatives [49–51]. These include selective serotonin receptor inhibitors (SSRIs) and alpha-2 adrenergic agonists, such as clonidine [51]. While beyond the scope of this article, several of these therapies have demonstrated considerable efficacy at improving vasomotor symptoms when compared to placebo. Randomized trials on SSRIs use in the treatment of vasomotor symptoms are summarized in Table 4 [52–56]. An important consideration in breast cancer survivors receiving adjuvant tamoxifen is that SSRIs reduce the metabolism of tamoxifen to its most active metabolite, endoxifen, by inhibition of the cytochrome P450 enzyme, CYP2D6. Caution is not needed when prescribing SSRIs to those on aromotase inhibitors, however.

Recommendations:

- Although not as effective as HRT in the treatment of vasomotor symptoms, SSRIs and alpha-2 adrenergic agonists are reasonable alternatives (Level I evidence).

Complementary and alternative approaches to menopause

Widespread complementary and alternative medicine (CAM) use has been reported among cancer patients with menopausal symptoms [57–61]. Specifically, in a patient survey study, von Gruenigen et al. demonstrated that 56% of gynecologic cancer survivors used CAMs, with ovarian and endometrial cancer survivors more likely to do so [61]. Therapies included nutritional supplements (20%), prayer (17%), exercise (12%), megavitamins (10%), and green tea (10%). While 69.5% believed CAM to be beneficial, only 31.6% discussed these therapies with their physician and felt their post-cancer treatment symptomatology was not being adequately addressed.

Although theoretically reasonable to consider as a possible remedy for menopausal symptoms in cancer survivors, there are problematic issues with CAM use in this setting. Dosages of active ingredients vary among preparations, many CAM products are not regulated by the Food and Drug Administration, and studies have provided conflicting evidence regarding the efficacy of these therapies. Most therapies contain phytoestrogens, non-steroidal compounds with some estrogen receptor activity that are found in soy, beans, fruits and flaxseed. The biologic effects of phytoestrogens are mediated through their active metabolites genistein, daidzein, and glycitin [62]. Although two studies demonstrated modest improvements in bone health, lipid levels and hot flashes with genistein, most randomized clinical trials of phytoestrogen therapy have not shown improvements in menopausal symptoms above that of placebo [62–72].

Another common CAM is the North American herb black cohosh (*Actaea racemosa*, *Cimicifuga racemosa*) [62]. The active compound binds to estrogen receptors as a result of selective estrogen receptor modulation [64]. Again, studies have produced conflicting data regarding its effectiveness in relieving vasomotor symptoms in postmenopausal women. A European study of 122 women with climacteric symptoms who were treated with an extract of black

Table 4
randomized studies of selective serotonin receptor inhibitor use in the treatment menopausal vasomotor symptoms.

Drug class	Most commonly used agent	Mode of action	Clinical trial	Trial findings
SSRI	Paroxetine, venlafaxine, and fluoxetine	Modulation of serotonin neurotransmitter pathways	Stearns et al.'s crossover study of 279 women, 151 of which were randomized to receive paroxetine + placebo or placebo + paroxetine for 8 weeks [51].	Paroxetine associated with a significant improvement in hot flashes and sleep.
			Stearns et al.'s study of 165 women randomized to receive controlled release paroxetine or placebo for 6 weeks [52].	Paroxetine associated with significant reductions in hot flash frequency of 64.6% compared to 37.8% with placebo use.
			Evans et al.'s study of 80 women randomized to receive extended release venlafaxine or placebo for treatment of hot flushes [53].	Venlafaxine reduced patient-reported effects of hot flushes on daily living, but did not have significant benefit on diary recorded severity of hot flushes.
			Loprinzi et al.'s comparison study of 218 women randomized to receive single dose intramuscular medroxyprogesterone acetate (MPA) or venlafaxine for six weeks [54].	Single dose MPA associated with statistically significant 79% reduction in hot flash scores compared to 55% reduction with venlafaxine.
			Loprinzi et al.'s crossover study of 81 women at increased risk of breast cancer, randomized to receive fluoxetine + placebo or placebo + fluoxetine for 8 weeks [55].	Fluoxetine resulted in significantly reduced severity and frequency of hot flashes.

cohosh or placebo [64] showed a beneficial effect in reducing hot flashes. However, two larger randomized studies, including the Herbal Alternatives for Menopause Trial (HALT), showed that there was no change in vasomotor symptoms, vaginal dryness or levels of follicle stimulating hormone levels among women taking black cohosh and soy containing botanicals when compared to placebo [65,66].

Recommendations:

- There is little evidence to support medicinal CAM use for menopausal symptom control.
- Exercise, non-medicinal CAMs, and genistein use may be considered in select circumstances.
- Black cohosh cannot be recommended for the amelioration of vasomotor symptoms in menopausal gynecologic cancer survivors (Level I evidence).

Conclusions

The decision to use hormone replacement therapy in women with gynecologic cancer pits the desire to achieve acceptable menopausal symptom control and optimize quality of life against the risks of stimulating quiescent neoplastic disease. Despite the limitations of retrospective and prospective observational studies and the need for more randomized trials, current evidence suggests that short-term HRT does not appear to have an adverse effect on oncologic outcome in most gynecologic cancer survivors and improves quality of life. HRT use does not appear to increase the risk of breast cancer in BRCA 1/2 mutation carriers who do not have a personal history of ER/PR positive breast cancer, nor does it nullify the breast/ovarian cancer risk-reducing effects of RRSO. Women with low-grade, early-stage endometrial cancer, cervical cancer and ovarian cancer with no other absolute contraindications for HRT are also potential candidates for this therapy. HRT should be avoided in women with ER/PR positive breast cancer and used with caution in those with incompletely resected ER/PR ovarian cancer. Conventional, non-hormonal therapies such as the SSRIs are moderately effective for the treatment of vasomotor symptoms; however, medicinal CAMs have no proven benefit in this regard and should be approached with caution in gynecologic cancer survivors.

Conflict of interest statement
The authors declare that there are no conflicts of interest.

References

[1] Jemal A, Siegel R, Xu J, Ward E. Cancer statistics. 2010 Sep–OctCA Cancer J Clin 2010;60(5):277–300.
[2] Wright JD. Safety of ovarian preservation in premenopausal women with endometrial cancer. J Clin Oncol Mar. 10 2009;27(8):1214–9 Epub 2009 Jan 26.
[3] Burger C, Van Leeuwen, Scheele F. Hormone replacement therapy in women treated for gynaecologic malignancy. Maturitas 1999;32:69–76.
[4] Belchetz P. Hormonal treatment of post-menopausal women. N Engl J Med 1994;330:1062–5.
[5] Woods N, Mitchell E. Symptoms during the perimenopause: prevalence, severity, trajectory, and significance in women's lives. Am J Med 2005;118:14–8.
[6] Hinds L, Price J. Menopause, hormone replacement and gynaecologic cancers. Menopause Int 2010;16:89–93.
[7] Parker W, Broader M, Chang E. Ovarian conservation at the time of hysterectomy and long-term health outcomes in the Nurses Health Study. Obstet Gynecol 2009;113(5):1027–37.
[8] Domchek S, Friebel T, Singer C. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA 2010;304(9): 967–75.
[9] Cohen L. Cancer treatment and the ovary. The effects of chemotherapy and radiation. Ann NY Acad Sci 2008;1135:123–5.
[10] Green D, Sklar C, Boice J, Mulvihill J, Whitton J, Stovall M, et al. Ovarian failure and reproductive outcomes after childhood cancer treatment: results from the Childhood Cancer Survivor Study. J Clin Oncol 2009;27:2374–81.
[11] Sklar C. Maintenance of ovarian function and risk of premature menopause related to cancer treatment. J Natl Cancer Inst Monogr 2005;34:25–7.
[12] Wallace WH, Thomson AB, Kelsey TW. The radiosensitivity of the human oocyte. Hum Reprod 2003;18:117–21.
[13] Hershlag A, Schuster M. Return of fertility after autologous stem cell transplantation. Fertil Steril 2002;77:419–23.
[14] Farquhar C, Marjoribanks J, Lethaby A, Suckling JA, Lamberts Q. Long term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database Syst Rev 2009(2):CD004143.
[15] Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 1998;280:605–13.
[16] Grady D, Herrington D, Bittner V, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy. Heart and Estrogen/Progestin Replacement Study follow-up (HERS II). JAMA 2002;288:49–57.
[17] Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. JAMA 2002;288: 321–33.
[18] The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. The Women's Health Initiative Randomized Controlled Trial. JAMA 2004;291:1701–12.
[19] Rebbeck T, Kauff N, Domchek S. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA 2 mutation carriers. J Natl Cancer Inst 2009;101:80–7.
[20] Finch A, Metcalfe KA, Chiang JK, Elit L, McLauglin J, Springate C, et al. The impact of prophylactic salpingo-oophorectomy on menopausal symptoms and sexual function in women who carry a BRCA mutation. Gynecol Oncol, Article in Press, 2010
[21] Armstrong K, Schwartz J, Randall T, Rubin S, Weber B. Hormone replacement therapy and life expectancy after prophylactic oophorectomy in women with BRCA1/2 mutations: a decision analysis. J Clin Oncol 2004;22:1045–54.
[22] Rebbeck T, Friebel T, Wagner T, et al. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA 1 and BRCA 2 mutation carriers: the PROSE Study Group. J Clin Oncol 2005;23:7804–10.
[23] Kauff N, Domchek S, Friebel T, et al. Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: a multi-center, prospective study. J Clin Oncol 2008;26:1331–7.
[24] Eisen A. Lubinski J., Moller P., et al. Hormone therapy and the risk of breast cancer in BRCA 1 mutation carriers. J Natl Cancer Inst 2008;100:1361–7.
[25] American College of Obstetrics and Gynecology Bulletin #89. Elective and risk-reducing salpingo-oophorectomy. Obstet Gynecol 2008;111:231–41.
[26] Holmberg L, Anderson H. HABITS (hormonal replacement therapy after breast cancer — is it safe?), a randomized comparison: trial stopped. Lancet 2004;363: 453–5.
[27] Weissman S, Bellcross C, Bittner C, et al. Genetic counseling considerations in the evaluation of families for Lynch syndrome. A review. J Gene Couns 2010 e-Publication ahead of print.
[28] Schmeler K, Lynch H, Chen L, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med 2006;354:261–9.
[29] Ferreira A, Westers H, Albergaria A. Estrogens, MSI, and Lynch syndrome-associated tumors. Biochim Biophys Acta 2009;1796(2):194–200.
[30] Gallup D, Stock R. Adenocarcinoma of the endometrium in women 40 years of age or younger. Obstet Gynecol 1984;64:417–20.
[31] Whitaker G, Lee R, Benson W. Carcinoma of the endometrium in young women. Mil Med 1986;151:25–31.
[32] Creasman WT, Henderson D, Hinshaw W, Clarke-Pearson DL. Estrogen replacement therapy in the patient treated for endometrial cancer. Obstet Gynecol 1986;67:326–30.
[33] Lee R, Burke T, Park R. Estrogen replacement therapy following treatment for stage I endometrial carcinoma. Gynecol Oncol 1990;36:189–91.
[34] Suriano KA, McHale M, McLaren CE, Li KT, Re A, DiSaia PJ. Estrogen replacement therapy in endometrial cancer patients: a matched control study. Obstet Gynecol 2001;97:555–60.
[35] Barakat R, Bundy B, Spirtos N, Bell J, Mannel R. Randomized double-blind trial of estrogen replacement therapy versus placebo in stage I or II endometrial cancer: a Gynecologic Oncology Group study. J Clin Oncol 2006;24:587–92.
[36] Coughlin S, Giustozzi A, Smith S, Lee N. A meta-analysis of estrogen replacement therapy and risk of epithelial ovarian cancer. J Clin Epidemiol 2000;53:367–75.
[37] Anderson G, Judd H, Kaunitz A, et al. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. JAMA 2003;290:1739–48.
[38] Morch L, Lokkegaard E, Andreasen A, et al. Hormone therapy and ovarian cancer. JAMA 2009;302(3):298–305.
[39] Bebar S, Ursic-Vrscaj M. Hormone replacement therapy after epithelial ovarian cancer treatment. Eur J Gynecol Oncol 2000;21:192–6.
[40] Eeles R, Wiltshaw E, Fryatt I, A'Hern R, Shepherd J, Harmer C, et al. Hormone replacement therapy and survival after surgery for ovarian cancer. BMJ 1991;302: 262–5.
[41] Guidozzi F, Daponte A. Estrogen replacement therapy for ovarian carcinoma survivors. Cancer 1999;86:1013–8.
[42] Schlumbrecht MP, Sun CC, Wong KN, Broaddus RR, Gershenson DM, Bodurka DC. Clinicodemographic factors influencing outcomes in patients with low-grade serous ovarian carcinoma. Cancer Feb. 11 2011, doi:10.1002/cncr.25929 Epub ahead of print.
[43] Mascarenhas C, Lambe M, Belloco R, Bergfelt K, Riman T, Persson I, et al. Use of hormone replacement therapy before and after ovarian cancer diagnosis and ovarian cancer survival. Int J Cancer 2006;119:2907–15.
[44] Lacey J, Brinton L, Barnes W, Gravitt P, Greenberg M, Hadjimichael O, et al. Use of hormone replacement therapy and adenocarcinomas and squamous cell carcinomas of the uterine cervix. Gynecol Oncol 2000;77:149–54.

[45] Martin J, Hahnel R, McCartney A, De Klerk N. The influence of estrogen and progesterone receptors on survival in patients with carcinoma of the uterine cervix. Gynecol Oncol 1986;23:329–35.
[46] Bodner K, Laubichler P, Kimberger O, Czerwenka K, Zeillenger R, Bodner-Adler B. Oestrogen and progesterone receptor expression in patients with adenocarcinoma of the uterine cervix and correlation with various clinicopathological parameters. Anticancer Res 2010;30:1341–6.
[47] Brand A, Bull C, Cakir B. Vaginal stenosis in patients treated with radiotherapy for carcinoma of the cervix. Int J Gynecol Cancer 2006;16:288–93.
[48] Ploch E. Hormonal replacement therapy in patients after cervical cancer treatment. Gynecol Oncol 1987;26:169–77.
[49] Martin R, Wheeler B, Metcalf C, Gunnell D. What was the immediate impact on population health of the recent fall in hormone replacement therapy prescribing in England? Ecological study. J Public Health Oxf 2010 e-Publication ahead of print.
[50] Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. JAMA 2004;291:47.
[51] Haas JS, Kaplan CP, Gerstenberger EP, Kerlikowske K. Changes in the use of postmenopausal hormone therapy after publications of clinical trial results. Ann Intern Med 2004;140:184.
[52] Stearns V, Slack R, Greep N, et al. Paroxetine is an effective treatment for hot flashes: results from a prospective randomized clinical trial. J Clin Oncol 2005;23:6919–30.
[53] Stearns V, Beebe K, Iyengar M, Dube E. Paroxetine controlled release in the treatment of menopausal hot flashes. A randomized controlled trial. JAMA 2003;289:2827–34.
[54] Evans M, Pritts E, Vittinghoff E, et al. Management of postmenopausal hot flushes with venlafaxine hydrochloride: a randomized, controlled trial. Obstet Gynecol 2005;105:161–6.
[55] Loprinzi C, Levitt R, Barton D, et al. Phase III comparison of depomedroxyprogesterone acetate to venlafaxine for managing hot flashes: North Central Cancer Treatment Group trial N99C7. J Clin Oncol 2006;24:1409–14.
[56] Loprinzi C, Sloan J, Perez E, et al. Phase III evaluation of fluoxetine for treatment of hot flashes. J Clin Oncol 2002;20:1578–83.
[57] Nedrow A, Miller J, Walker M, et al. Complementary and alternative therapies for the management of menopause-related symptoms. A systematic evidence review. Arch Intern Med 2006;166:1453–65.
[58] Newton K, Buist D, Keenan N, et al. Use of alternative therapies for menopause symptoms: results of a population-based survey. Obstet Gynecol 2002;100:18–25.
[59] McKay D, Bentley J, Grimshaw R. Complementary and alternative medicine in gynaecologic oncology. J Obstet Gynaecol Can 2005;27:562–8.
[60] Mueller C, Mai P, Bucher J, et al. Complementary and alternative medicine use among women at increased genetic risk of breast and ovarian cancer. BMC Compl Alt Med 2008;8:17.
[61] von Gruenigen VE, White LJ, Kirven MS, Showalter AL, Hopkins MP, Jenison EL. A comparison of complementary and alternative medicine use by gynecology and gynecologic oncology patients. May–JunInt J Gynecol Cancer 2001;11(3): 205–9.
[62] Jacobs A, Wegewitz U, Sommerfeld C, et al. Efficacy of isoflavones in relieving vasomotor menopausal symptoms — a systematic review. Mol Nutr Food Res 2009;53:1084–97.
[63] Borrelli F, Ernst E. Black cohosh (*Cimicifuga racemosa*) for menopausal symptoms: a systematic review of its efficacy. Pharmacol Res 2008;58:8–14.
[64] Frei-Kleiner S, Schaffner W, Rahlfs V, et al. *Cimicifuga racemosa* dried ethanolic extract in menopausal disorders: a double-blind placebo-controlled clinical trial. Maturitas 2005;51:397–404.
[65] Reed S, Newton K, LaCroix A, et al. Vaginal, endometrial, and reproductive hormone findings: randomized, placebo-controlled trial of black cohosh, multibotanical herbs, and dietary soy for vasomotor symptoms: the Herbal Alternatives for Menopause (HALT) study. Menopause 2008;15:51–8.
[66] Pockaj B, Gallagher J, Loprinzi C, et al. Phase III double-blind, randomized, placebo-controlled crossover trial of black cohosh in the management of hot flashes: NCCTG trial N01CC. J Clin Oncol 2006;24:2836–41.
[67] Brink E, Coxam V, Robins S, et al. Long-term consumption of isoflavone-enriched foods does not affect bone mineral density, bone metabolism, or hormonal status in early postmenopausal women: a randomized, double-blind, placebo controlled study. Am J Clin Nutr 2008;87:761–70.
[68] Allen J, Becker D, Kwiterovich P, et al. Effect of soy protein-containing isoflavones on lipoproteins in postmenopausal women. Menopause 2007;14:106–14.
[69] Atteritano M, Marini H, Minutoli L, et al. Effects of the phytoestrogen genistein on some predictors of cardiovascular risk in osteopenic, postmenopausal women: a two-year randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab 2007;92(8):3068–75.
[70] Albertazzi P, Steel A, Bottazzi M. Effect of pure genistein on bone markers and hot flushes. Climacteric 2005;8:371–9.
[71] Atkinson C, Compston J, Day N, et al. The effects of phytoestrogen isoflavones on bone density in women: a double-blind, randomized, placebo-controlled trial. Am J Clin Nutr 2004;79:326–33.
[72] Unfer V, Casini M, Costabile L, et al. Endometrial effects of long-term treatment with phytoestrogens: a randomized, double-blind, placebo-controlled study. Fertil Steril 2004;82:145–8.