Hormone therapy for postmenopausal endometrial cancer survivors: a survey among Greek obstetricians-gynaecologists

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Summary

Purpose of investigation: In this study we evaluated the prescription attitude of Greek obstetricians-gynaecologists towards hormone replacement therapy (HRT) for endometrial cancer survivors. *Methods:* An anonymous questionnaire was sent to 900 members of the Hellenic Society of Obstetrics and Gynaecology, presenting a hypothetical case of an endometrial cancer survivor with indications for HRT, followed by a series of relevant questions. *Results:* Three hundred and three valid responses were received and analysed according to age, gender and practice setting. HRT would be prescribed by 30.4% of gynaecologists; as far as type of regimen is concerned, 67.4% would prescribe tibolone, 22.8% estrogen-only and 9.8% estrogen plus progestagen. In contrast, 69.6% would not prescribe HRT due to the fear of endometrial cancer recurrence (88.2%), development of breast cancer (2.8%) or both (4.7%); among them, 28.4% would prescribe central nervous system (CNS) medications, selective estrogen receptor modulators (SERMs), phyto-oestrogens or biphosphonates, as alternates. *Conclusions:* One out of three Greek gynaecologists would prescribe HRT to endometrial cancer survivors. Alternative therapies, mainly CNS medications, would be suggested by the opposers.

Key words: Endometrial cancer survivors; Hormone replacement therapy; Tibolone; Estrogen replacement therapy; Estrogen-progestogen combination; Prescription attitude.

Introduction

Endometrial cancer (EC) is the most common gynaecologic cancer. It is most frequently diagnosed in postmenopausal women (median age 63 years) [1], even though 20-25% of cases occur before menopause [2]. The majority of the cases are of early stage. Treatment of EC in premenopausal women (total hysterectomy with bilateral salpingo-oophorectomy and, in selected cases, radio- or chemotherapy) results in iatrogenic menopause and estrogen deficiency states, such as hot flushes or osteoporosis.

Since the 5-year survival rate for Stage I EC is over 80% [1], the women are expected to live many years in a postmenopausal state. Hormone replacement therapy (HRT) might improve their quality of their life, targeting climacteric symptoms and osteoporosis. As the most common form of EC is the endometriod type, which is estrogen-dependent, the medical community, until the 1990s, considered that HRT was contraindicated in EC survivors [3]. Despite this belief, data from clinical studies have failed to show an increased risk of EC recurrence or mortality in case of HRT use by EC survivors [4-11].

The aim of the present study was to investigate the attitude of Greek obstetricians-gynaecologists towards prescription of HRT or an alternative therapy as treatment for menopausal symptoms in EC survivors.

Materials and Methods

A questionnaire was sent to 900 obstetricians-gynaecologists, members of the Hellenic Society of Obstetrics and Gynaecology, out of a total of 2,700 at the time of the study (April 2009). The selection was random from the society's register (every third registered member was selected). The questionnaire was anonymous and its first part included demographic data: age, gender and type of practice [academic center, National Health System (NHS) hospital, private practice]. The second part included a hypothetical case of a patient with a history of EC followed by a series of relevant questions. This study was part of a more extended one concerning cases of cervical, endometrial, ovarian and breast cancer survivors.

The following case was presented: a 52-year-old female Caucasian, para 2 was treated at the age of 49 (being premenopausal) with abdominal hysterectomy plus bilateral salpingo-oophorectomy for a well differentiated EC of endometrioid type (FIGO Stage IA, grade I). Since then (i.e., three years ago), clinical laboratory and imaging follow-up were negative for recurrence. The woman was complaining of menopausal symptoms (hot flushes, night sweats, vaginal dryness and libido impairment), while a bone densitometry revealed osteopenia. The gynecologists were asked (1) whether they would prescribe HRT (closed-type answer: "yes" or "no"), (2) if yes, which hormonal regimen they would prefer to prescribe (closed-type answer: "estrogen-only", "estrogen/progesterone combination", "tibolone" or "selective estrogen receptor modulators (SERMs)" and (3) if not, why (open-type answer) and (4) which (open-type answer) alternative therapy they would suggest.

The questionnaire was based on a similar one by Rozenberg *et al*. [12] although modifications were taken place. The chi-square test was used to define differences among the groups. Data were analysed by the use of SPSS for Windows, version 11 (SPSS Inc., IL, USA).

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Results

A total of 303 responses to the questionnaire were collected, all with valid answers (overall response rate: 33%). Regarding the type of practice, 11.6% (n = 35) were working in an academic center, 23.7% (n = 72) in an NHS hospital and 64.7% (n = 196) in private practice. A percentage of 81.5 (n = 247) were males and the remaining 18.5% (n = 56) females. Finally, 48.9% (n = 148) of the responders were younger than 48 years of age and classified as "younger gynaecologists" and 51.1% (n = 155) as "older". The cut-off point of 48 years was chosen as it represented the mean age of the responders.

In the first question "Would you prescribe HRT in an EC survivor?", 30.4% answered "yes" (n = 92) and 69.6% "no" (n = 211). Gynaecologists working in an academic center answered "yes" in a greater proportion (50.4%) than their colleagues working in an NHS hospital (15.3%) or in private practice (33.0%) ($p < 0.001$). As far as age is concerned, "younger gynecologists" were willing to prescribe HRT in a greater proportion (40.5%) than their "older colleagues" (19.5%) ($p < 0.001$). Finally, there was no significant difference as far as gender was concerned.

In the second question "If yes, which hormonal regimen would you prefer?", 67.4% would prescribe "tibolone" (n = 62), 22.8% "estrogen-only" (n = 21) and 9.8% "estrogen plus progestagen" (n = 9) ($p < 0.05$). There were no significant differences regarding age, gender or type of practice.

In the third question, "If no, why?", among those who were not willing to prescribe HRT (n = 211), 88.2% would do so because of the fear of EC recurrence (n = 186), 2.8% because of the fear of development of breast cancer (n = 6), 4.7% for both reasons (n = 10) whereas (4.3%) did not answer (n = 9). There were no significant differences regarding to age, gender or type of practice.

In the fourth question, "If not, which alternative treatment would you suggest?", the majority (71.6%) of the participants, regardless of age, gender or type of practice, were not willing to prescribe any medication at all (academic center: 70.6%, NHS hospital: 86.9% and private practice: 64.7%, p = NS). This unwillingness was apparent regardless of age group ("younger": 68.2% vs "older": 68.9%, p = NS) or gender (males: 70.5% vs females: 73.2%, p = NS). A minority would offer other treatment options, such as central nervous system (CNS) medications (21.3%), phyto-estrogens, biphosphonates, or SERMs (in total 7.1%).

Discussion

According to the results of this study, two out of three Greek obstetricians-gynaecologists are reluctant to prescribe HRT to EC survivors. Tibolone is the preferred regimen by the majority of gynaecologists who are in favor of HRT. The fear of EC recurrence is stated by the vast majority as the main reason for not prescribing HRT. Finally, the gynaecologists who avoid prescribing HRT in women with a history of EC prefer to prescribe no regimen at all or alternative medications, such as CNS drugs for the treatment of vasomotor symptoms.

Until the 1990s, HRT was contraindicated for menopausal symptoms in women treated for EC, as this neoplasia is usually estrogen-dependent [13]. This attitude was based on the theoretical risk that oestrogens may trigger carcinogenesis in patients with EC, despite the fact that data from well-designed randomized trials were inconclusive. Given the lack of evidence for detrimental effects of HRT on EC survivors, the American College of Obstetricians and Gynecologists (ACOG) issued a Committee Opinion in 2000, stating that the decision to use HRT in these women should be individualised on the basis of potential benefits and risks [14].

A series of studies have addressed the issue of possible beneficial effect of HRT in EC survivors. In 1986, Creasman *et al*., in a case-control study, were the first to report that the administration of conjugated oestrogens in 47 women with Stage I disease had favourable effects [4]. Four other retrospective studies (three cohort [5, 6, 9] and one case-control [8]) reported on patients with a history of EC Stage I-III and found that the prescription of conjugated estrogens with or without progestagens did not increase the rate of recurrence or death. All these studies are limited by their retrospective design, small sample size and short follow-up period. In addition, in a case-control study [10], women with a previous history of EC, Stage I-II, received conjugated estrogens with or without medroxy-progesterone and showed no increase in recurrence rate or mortality. Finally, a randomized, double-blind, prospective trial of estrogen vs placebo [11], in surgical Stage I-II women, cannot conclusively refute or support the safety of estrogen treatment with regard to risk of EC recurrence.

To the best of our knowledge, there is only one similar study concerning the prescription attitude of Belgian gynaecologists, which showed that two out of three professionals would prescribe HRT to a woman with a history of early stage EC, no signs of recurrence and indications for HRT [12]. On the contrary, in our study, only one out of three Greek gynaecologists was willing to prescribe hormonal regimens in EC survivors. It is noteworthy that the aforementioned Belgian study was published before the results of the Women's Health Initiative study (WHI) [15] and Million Women Study (MWS) [16], which dramatically changed the prescription attitude. Although there are no previous published data in the Greek literature, it seems reasonable to postulate that the results of the WHI and MWS studies had a negative impact on the prescription attitude. In addition, the absence of official guidelines on HRT prescription issued by the Hellenic Society of Obstetricians and Gynaecologists might play a role in refraining gynaecologists from prescribing HRT due to the fear of malpractice. Moreover, in Greece there is a widely held misconception among women of a possible association between use of exogenous sex hormones and cancer.

Another finding of our study is the fact that tibolone was the preferred hormonal regimen for women with a

history of early Stage EC. This could be attributed to the knowledge that tibolone is being converted to a Δ-4 androstenedione metabolite in the endometrium, which has no estrogenic activity [17, 18]. Nevertheless, the MWS reported significantly increased risk for EC in users of tibolone at an incidence rate of six cases per 1,000 women over a period of five years [16].

Interestingly, gynaecologists working at academic centers as well as younger colleagues most usually prescribe HRT in comparison to other groups of colleagues. This could be explained by the fact that gynaecologists of academic centers more closely follow the rapid progress of science on this issue; in a similar way, younger gynaecologists are, usually, better informed as they have recently completed their training.

The limitations of our study include the facts that the questionnaire was sent only to a subgroup of Greek gynaecologists (33%) and the response rate was rather low (33%). Nevertheless, the randomly selected subgroup (every third registered member was selected) weakens the first limitation.

In conclusion, the majority of obstetricians-gynaecologists practicing in Greece would not prescribe HRT for relief of menopausal symptoms in EC survivors due to the theoretical risk of disease relapse. Tibolone is the preferable regimen among those who are willing to prescribe hormonal therapy. The majority of the gynaecologists who would not prescribe hormonal therapy suggest either no medication at all or the use of CNS regimens.

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