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Critical comment

HRT and gynaecologic cancer after WHI: old stuff or new doubts?

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Abstract

Previous studies had shown that there is little concern about endometrial cancer risk with hormone replacement therapy (HRT), whereas the risk of ovarian cancer is still debated.

A new paper based on the women's health initiative (WHI) study devoted to gynaecologic cancers has been published in the October 2003 issue of JAMA, leading to the conclusion that also for endometrial and ovarian cancer risk, as the first WHI publication did for breast cancer risk, the previous large studies have been confirmed.

About follow-up the authors conclude that, "The increased burden of endometrial biopsies required to assess vaginal bleeding further limits the acceptability of this regimen."

These conclusions deserve a thorough analysis and must be read in the light of the burden of available epidemiological and clinical data and of recommended clinical practice.

In the WHI trial the use of continuous combined HRT has resulted in a considerable increase of both imaging and invasive exams, to investigate women with bleeding or spotting, but the findings of these exams have been invariably negative.

As far as, all published studies agree on the fact that continuous combined HRT either has no effect or significantly reduces the risk of both endometrial hyperplasia and cancer, there should be no reason to close-watching endometrium of women using this regimen with a different strategy from that employed on any healthy woman.

Keywords: Gynaecologic cancer; Hormone replacement therapy; Endometrial biopsy

1. Introduction

A new paper based on the women's health initiative (WHI) study devoted to gynaecologic tumour risk and follow-up procedures in women taking estrogens and progestins has been published in the October 2003 issue of JAMA [1].

Previous studies and clinical experience had shown that there is little concern about endometrial cancer risk with continuous combined treatment, whereas the risk of ovarian cancer is still debated due to conflicting and inconclusive results.

A careful reading of the Anderson's paper leads to the conclusion that also for endometrial and ovarian cancer risk, just as the first WHI publication did for breast cancer risk [2], the data of the previous large observational studies have been confirmed.

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A quick reading of the summary could instead insinuate in the reader alarming suggestions. The conclusion in the author's summary is that: "continuous combined estrogen plus progestin therapy may increase the risk of ovarian cancer, while producing endometrial cancer rates similar to placebo."

About follow-up the authors conclude that "the increased burden of endometrial biopsies required to assess vaginal bleeding further limits the acceptability of this regimen. These data provided additional support for caution in the use of continuous combined hormones."

These conclusions deserve a thorough analysis and must be read in the light of the burden of available epidemiological and clinical data and of recommended clinical practice.

2. Endometrial cancer

The positive correlation between estrogen intake and the risk of endometrial cancer and hyperplasia has been recognised for over 30 years. In the metanalysis by Grady et al. the overall RR for estrogen only (ERT) users compared to never-users is 2.3 (95% CI 2.1–2.5); the magnitude of risk is correlated to the dose and the duration of treatment and is nine-fold higher for treatments lasting longer than 10 years [3]. However, the addition of progestin at adequate dosage substantially reduces the risk of developing endometrial cancer [4]. Indeed, in the same metanalysis, the RR for women treated with estrogens plus progestins overlaps that of the untreated population (RR = 0.8; 95% CI 0.6–1.2) [3].

The WHI trial confirms that progestin protect against the increased risk of endometrial cancer associated with unopposed estrogen [1,2]. In the WHI study a small non-significant reduction in endometrial cancer risk was observed with estrogen plus progestin use in a continuous combined regimen (HR = 0.81; 95% CI 0.48–1.36). In this group of women the incidence of endometrial cancer during the 5.6 years of follow-up was 56 per 100,000 person-years, 13 cases per 100,000 person-years less than observed in women taking placebo, and even lower as compared to the observed incidence rate of 83 per 100,000 person-years reported by SEER in general population.

All the recent studies substantiate the neutrality or even a protective effect of continuous combined HRT regimen on the endometrium [5–8]. This is true also for long-term treatments, as shown by a recent American study who didn't show any increase of endometrial cancer risk among women treated with continuous combined regimen (RR = 1.07; 95% CI 0.80–1.43 for more than 5 years of use) [5]. In a Swedish study the RR with continuous combined therapy is significantly reduced (RR = 0.2; 95% CI 0.1–0.8) [6]. In a case-control study carried out in Washington, continuous combined HRT had a RR of endometrial cancer of 0.6 (95% CI 0.3–1.3) compared with women who had never used hormones, and users of this type of regimen had a risk that was 0.4 times that of women treated with sequential regimens with progestogen for 10 to 24 days [7].

Sequential regimen for long periods of treatment has generated some worries and doubts [7,8].

An increased risk of 2.5 (95% CI 1.1–5.5) has been reported by an American study among women treated with sequential HRT for more than 5 years [8]. Moreover, in the aforementioned Swedish study the use of HRT with sequential progestin association (most commonly 10 days per cycle) for more than 5 years leads to a significant increase of endometrial cancer risk (RR = 2.9; 95% CI 1.8–4.6); this is confined to progesterone derived progestins: RR = 3.2 (95% CI 1.7–6.0), whereas with testosterone derived progestins the RR is 0.9 (95% CI 0.5–1.5) [6].

Other authors did not confirm these data. In a large American study, women treated with cyclic sequential HRT regimen, with progestins for at least ten days per month, do not have a significant increase of endometrial cancer risk, also after 5 years of use: RR = 1.07 (95% CI 0.82–1.41) [5].

Anderson in its paper emphasises the need to perform active follow-up, with instrumental and invasive procedures, of women taking HRT [1]. Endometrial evaluation by endometrial biopsy was performed on every women in WHI trial prior to randomisation; furthermore, a 5% cohort of women was randomly selected to undergo routine biopsies during follow-up at years 3, 6, and 9. Endometrial biopsies were performed by trained staff including physicians and nurse practitioners and readings were obtained by local pathologists. During follow-up, women with persistent or heavy bleeding were evaluated by a gynaecologist and,

if indicated, submitted to endometrial biopsy. Only when biopsies could not be accomplished, vaginal ultrasound of the uterus was performed. Dubbel endometrium thickness of greater than 0.5 cm was considered pathological and resulted in discontinuation of study.

Among women selected for usual care, endometrial biopsy was requested in over one third of subjects, more than five times higher than in the placebo group. Histological data was reassuring: in fact in the cohort of women selected for routine endometrial surveillance, HRT reduced the percentage of unsuccessful biopsies (21% versus 36% in the placebo group) and no difference was observed in the distribution of histological findings in the two groups.

The authors observe that uterine bleeding is a frequent adverse effect of continuous combined regimen, leading to much more frequent biopsies and ultrasound examination and, in several cases, also to hysterectomy. This approach is unusually aggressive and to our opinion a significant over use of diagnostic procedures and over treatment (at least according to European standards) can be recognised. This is possibly due to the difference existing between a controlled clinical trial and the clinical practice. The unusually high (33%) rate of endometrial biopsies performed in the WHI study can be justified within the frame of a trial both to obtain safety data and to protect the investigators from legal litigations. In clinical practice, in the follow-up of women taking HRT, this would never happen, more than ever in women who have had a thorough basal endometrium evaluation just prior to HRT administration, as in the WHI trial. The high rate of endometrial bleeding in the first few months of treatment with continuous combined HRT, in the absence of any endometrial abnormality, is well known and does not require, in the short time, any further evaluation.

Hopefully, the problem of endometrial bleeding will be less and less frequent in the future: the tendency towards low-dose regimens [9–11], in which both estrogen and progestin are given at reduced doses, long-cycle regimens [12,13], in which progestin is given at longer intervals, or interrupted progestin regimen [14], in which estrogen is administered continuously and progestin is given in a 3-days on, 3-days off pulsed fashion, will be accompanied by a sharp reduction of this symptom.

All these schedules are associated with lower incidence of vaginal bleeding. Endometrial safety data on low doses of estro-progestin combinations, mainly referred to continuous combined regimens, are all encouraging [9–11]. The health, osteoporosis, progestin, estrogen (HOPE) study, comparing different continuous combined low-dose regimens with the same standard dose used in the WHI trial, had shown a higher proportion of women who experienced no bleeding in the first cycle with low-doses (ranging from 80 to 89%) as compared to standard dose (68.2%). However, vaginal bleeding is observed in 31.4% of women after 6 months of continuous combined treatment with standard dose and in 10–25% of women with low-dose. After 1 year of treatment a complete amenorrhoea is reported by 75% of women treated with standard dose and by 82–89% of women treated with low-dose continuous combined regimen [9].

Data on long-cycle regimens are not clear. Previous studies have provided reassuring results [15,16]. A subsequent study, on the contrary, was interrupted because of an excess of endometrial cancer and hyperplasia (6.2% versus 0.8% with standard regimen) [12]. These data have been confirmed by a recent Finnish study, which shows a higher risk of endometrial cancer in women receiving MPA 20 mg per day for 14 days every 3 months associated to estradiol valerate 2 mg per day as compared to standard regimen [13]. Possibly, the solution will be found by reducing the prescribed amount of estrogen. In the recent study by Ettinger, in fact 0.3 mg per day of CEE associated with 14-day course of MPA 10 mg per day every 6 months showed an acceptable rate of endometrial hyperplasia (1.6% after 1 year of treatment) [17].

To conclude with the follow-up strategy, we are somewhat surprised by that in the WHI study the first procedure used to asses vaginal bleeding is endometrial biopsy and ultrasound is used only when biopsy is not feasible (12.8% in HRT and 4% in placebo group). This is again different from everyday clinical practice (at least in Europe) where trans vaginal ultrasonography (TVUS) is the first line exam in the follow up of women taking HRT (because the condition to monitor is endometrial hyperplasia) and biopsy is performed only when endometrial thickness is above the safety limits of 4–5 mm or bleeding is lasting longer than a few months.

3. Ovarian cancer

In the WHI trial, during 5.6 years of follow-up 32 women were diagnosed as having invasive ovarian cancer [1]. The hazard ratio (HR) in the estrogen plus progestin group for invasive cancer was 1.64, not statistically significant (95% CI 0.78–3.45). The possibility of an increasing effect over time, suggested by the Kaplan Meier estimates, did not reach statistical significance. Ovarian cancer was the reported cause of death in nine women taking HRT and three women taking placebo (HR 2.70; 95% CI 0.73–10.0), again not statistically significant. There was no evidence of a difference between treatment and placebo groups in the distribution of histological type, grading or stage of disease at diagnosis.

In this trial, women taking estrogen plus progestin have invasive ovarian cancer at a rate of 42 per 100,000 person-years, 15 per 100,000 person-years more than placebo, but somewhat lower than the population-based rate of 45 per 100,000 person-years reported by the surveillance, epidemiology, and end results (SEER) registry for women of this age.

Data from the meta-analyses published in 90's and from more recent studies do not indicate a positive correlation between HRT and ovarian cancer, and the results are often inconsistent [18–22]. Also the impact of HRT duration on the risk is still debated. In the metanalysis by Garg et al. [21], the use of HRT for more than 10 years is associated to a RR of 1.27 (95% CI 1.00–1.61), whereas Coughlin et al. [20], in a recent meta-analysis on 15 studies does not report any association between HRT use and incidence of ovarian cancer. Moreover, in a reanalysis of four European control-matched studies on 1470 cases of ovarian cancers, only a weak positive association with the time of exposure to hormones was found: RR = 1.67 for treatment periods up to 2 years and 1.79 for a use longer than 2 years [22]. In 2002, three studies assessed the ovarian cancer risk associated to the type of HRT used, estrogens alone and estro-progestin in different combinations, but the results did not help to work out the controversies [23–25].

Unlike endometrium carcinoma, the aetiology of ovarian cancer is poorly understood and the possible role of oestrogen and progestin is uncertain [26]. This is confirmed by the many aetiologic hypothesis proposed during the years. They are sometimes conflicting, in the different hypothesis the same hormone can exert a potentially protective or detrimental effect, and the one that is best fitting is invoked to explain and support the result of a single epidemiological or clinical study.

The aetiologic hypothesis of recurring ovulations would explain the reduction of risk related to OC and repeated pregnancies. According to this hypothesis, every single ovulation would produce micro traumatic lesions inside the coelomic epithelium, which may eventually contribute to the subsequent development of ovarian cancer [27].

Another hypothesis accounts for the retrograde-transport of carcinogens by fallopian tubes [28] and allows for the allegedly increased risk with hormone use, namely with sequential regimens that cause regular cyclic bleeding beyond the menopause. In the Swedish study on 655 cases and 3899 controls, the only one to distinguish between sequential or continuous regimen, sequential HRT increases significantly the risk of developing ovarian cancer (RR = 1.54; 95% CI 1.15–2.05), though continuous combined HRT has no significant effect (RR = 1.02; 95% CI 0.73–1.43) [23].

WHI investigators underline that the majority of women in the Swedish study used a 19-nor-testosterone derived progestin rather than the 17-hydroxyprogesterone derivative medroxyprogesterone acetate used in the American trial, but do not clarify nor hypothesize the difference between these two compounds in relation to ovarian cancer risk. Unfortunately, the data of the estrogen only arm of the WHI study are not yet available.

Progestins have been hypothesized to have a favourable effect on ovarian cancer incidence, based on the lower risk associated with oral contraceptives and increased parity. Animal data also describe a role of progestins in promoting apoptosis [29]. The theory of the protective effect of progestins is corroborated by the studies showing a risk increase with estrogen only regimens but not with estrogen and progestin combinations like that used in the WHI study. Data from the breast cancer detection and demonstration project underline a significant increase of risk associated to the use of estrogen alone (RR = 1.6; 95% CI 1.2–2.0), also correlated to the duration of use (a 7% increase of risk per year of use); conversely estro-progestin HRT does not appear to be related

to any risk increase (RR = 1.1; 95% CI 0.64–1.7) for periods both longer and shorter than 2 years [25]. Also in the Swedish study, unopposed estrogens (RR = 1.43; 95% CI 1.02–2.0) and even vaginally delivered estrogens (RR = 1.33; 95% CI 1.03–1.72) seem to increase ovarian cancer risk, unlike oral estriol [23]. A further American case-control study published on 2002 does not observe any correlation between estrogen plus progestin therapy and ovarian cancer risk, but unlike the previous studies, it reports a protective effect of unopposed estrogens confined to hysterectomised women (RR = 0.17; 95% CI 0.04–0.82) [24].

Great uncertainty derives also from the studies that analysed the ovarian cancer mortality as related to HRT. Persson et al. did not observe any mortality increase among women taking HRT [30], while Rodrigeuz observed higher mortality among women treated for longer than 10 years (RR = 2.20) [31]. Despite the remarkable number of cases considered and the noteworthy observational period (14 years) of this latter study, data on HRT assumption for more than 10 years in this trial derived from only 66 cases of ovarian cancer and have been obtained with a self-administered questionnaire more than 20 years before.

4. Other gynaecologic cancers

In all participants to WHI trial, papanicolau smears were performed as a courtesy at 3 years intervals by the staff of the study and pathological analysis was obtained locally [1].

During the follow up only 13 cases of cervical cancer were diagnosed (eight in the HRT group and five in the placebo group), one case of non endometrial uterine cancer and seven cases of other gynaecologic tumors. Data are too sparse to provide meaningful comparisons. However, the HR for cancer of the cervix is 1.44 (95% CI 0.47–4.24), not statistically significant.

The only interesting result is a statistically significant increase in mild abnormalities detected on papanicolau tests: the proportion of women with a diagnosis of L-SIL during follow-up pap smears were 7.8% for estrogen plus progestin arm and 5.5% in the placebo arm. On the contrary, the proportion of women with severe cervical dysplasia (H-SIL) is similar in the two groups (0.3% and 0.4% respectively). These data warrants further investigation, because in the WHI study the reading of the smears was not centralized and the inter-observer variability, mainly in the adjudication of low-grade displasia, is well known.

5. Conclusion

WHI is the only prospective randomised placebo controlled study evaluating the effect of HRT also on risk of gynaecologic tumors. The data are consistent with today's understanding based on the several previous observational studies and their meta-analysis. Continuous combined HRT does not increase the risk of developing endometrial cancer.

It does neither significantly increase the risk of developing ovarian cancer, affect the stage of the disease at diagnosis, nor influence the risk of dying of this disease.

The study arm with estrogens only, who will help clarifying whether estrogens alone can have a different impact on ovarian cancer risk, as suggested by some small studies, is still ongoing.

In the WHI Study, the use of continuous combined HRT, has stimulated a considerable increase of the use of both imaging and invasive exams, in order to investigate women with bleeding or spotting. It must be underscored that there is no reason to close-watching endometrium of women using continuous combined HRT using a strategy different from that employed on any healthy woman, as far as all published studies agree on the fact that continuous combined HRT has either no effect or significantly reduces the risk of both endometrial hyperplasia and cancer.

Anderson's study confirms that there is no reason to investigate any case of endometrial bleeding during the first few months of continuous combined HRT, especially if a basal endometrial evaluation with negative result has been performed prior to starting the treatment.

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