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Tibolone and Endometrial Cancer

A Cohort and Nested Case-Control Study in the UK

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Abstract

Objective: Case series and spontaneous reports of endometrial cancer have raised the question as to whether the use of tibolone (introduced into the UK in 1991) is associated with an increased risk of endometrial cancer. This study set out to evaluate whether tibolone use is associated with an increased risk of endometrial cancer.

Methods: Age-adjusted incidence rate ratios (IRRs) of endometrial cancer were calculated for tibolone use compared with the use of other hormone replacement therapy (HRT). Separate sets of controls, matched for age and general practice, were compared with cases, all nested within a cohort of HRT users identified from the UK General Practice Research Database (GPRD). Conditional logistic regression analysis, adjusted for potential confounders, was used to study the association between tibolone use and the risk of endometrial cancer.

Results: 4995 women used tibolone as their first HRT product; 10 783 (4.3%) of the users of combined HRT had changed to tibolone at some time during the study period. Amongst women whose HRT began with tibolone, the age-adjusted IRR relative to those who started with combined sequential HRT was 1.83 (95% CI 1.19, 2.82). The nested case-control study comprised 162 cases, each matched to two sets of 972 controls. There were 43 tibolone-exposed subjects, 28 of whom had used other HRT before or after tibolone. The adjusted odds ratio of the risk of endometrial cancer in women who had ever used tibolone, compared with users of combined sequential HRT, was 1.54 (95% CI 1.03, 2.32) in the age-matched set and 1.58 (95% CI 1.01, 2.47) in the practice-matched set. Sensitivity analyses did not decrease the risk estimates found.

Discussion: Tibolone may be associated with an increased risk of endometrial cancer compared with conventional forms of HRT, but our data are fragile. Residual bias and uncontrolled confounding cannot be excluded, and follow-up time is insufficient to draw any firm conclusions with respect to the endometrial safety of tibolone.

Background

The first case series of women with endometrial pathology associated with tibolone (Livial®)[1] was published in 1994.[1] By December 2001, an unexpectedly high number of spontaneous reports of endometrial cancer amongst women using tibolone had been filed in the UK with the manufacturers or licensing authorities. The question arose as to whether tibolone is associated with an increased risk of endometrial cancer.

The annual incidence of endometrial cancer in England and Wales is approximately 9.6 per 100 000 women aged 45–49 years, rising to 50.3 per 100 000 women aged 60–64 years. Thereafter, rates tend to be stable.[2] The primary symptom is dysfunctional uterine bleeding. Survival rates vary with age and tumour stage at diagnosis; in Caucasian women 5-year survival is about 86%.[3] The known risk factors for endometrial cancer include unopposed estrogen use, tamoxifen use, diabetes mellitus, polycystic ovary disease, nulliparity, late menopause, early age at menarche, a high body mass index (BMI), presence of an estrogen-producing tumour, hypertension, gall bladder disease and a positive family history.[4-6] Many of these are associated with excess estrogen. In women with a uterus receiving estrogen replacement therapy, progestogens are added to therapy to reduce atypical endometrial hyperplasia, the precursor of endometrial adenocarcinoma.[7]

Tibolone is a synthetic corticosteroid licensed in the UK in 1991 for the alleviation of menopausal symptoms and for the prevention of osteoporosis in women with at least 1 year of amenorrhoea. It is structurally related to norethisterone and noretynodrel and exhibits weak estrogenic, progestogenic and androgenic properties combined in a single chemical substance. In the endometrium, it is metabolised by the enzyme 3β-hydroxysteroid dehydrogenase/isomerase into its Δ4 metabolite, which has higher progestogenic potency and is virtually devoid of estrogenic activity.[8] It is given continuously without added progestogen and does not cause monthly withdrawal bleeds typical of combined sequential hormone replacement therapy (HRT) − one of the main reasons for women to discontinue HRT use.[9] In 1998 it represented approximately 6% of the HRT market in the UK.[10] The estrogenic effect of tibolone on the endometrium is said to be similar to that of continuous combined HRT with respect to endometrial thickening, yet fewer women experience dysfunctional bleeding and spotting.[11] Endometrial proliferation is present in 10% of users after long-term treatment with tibolone.[12] In contrast, progestogenic properties of tibolone differ from combined sequential HRT: in previous studies, tibolone resulted in atrophic effects and endometrial regression, whereas the use of progestogens caused withdrawal bleeding.[12,13] We carried out an epidemiological study to determine whether women exposed to tibolone have an increased risk of endometrial carcinoma.

Methods

This investigation used the UK General Practice Research Database (GPRD).[14] The study period was 1 January 1992 to 1 March 1999. The GPRD contains the anonymised computer-generated medical records from primary care of approximately 6% of the UK population. It includes information on diagnoses and symptoms, hospital admissions and discharges, and prescriptions.[15,16] Details of HRT use in this population are described elsewhere.[10] The design of the investigation was a cohort study and a case-control study nested within a cohort of women using HRT.

Cohort Study

The cohort comprised all women aged 40–74 years without a record of a hysterectomy and who had been prescribed HRT at any time during the study period. Women who did not have any record of HRT use in the first 12 months of their registration on the database, but did thereafter, were assumed to be first time HRT users. Women started contributing person-time to the study and became

1 The use of trade names is for product identification purposes only and does not imply endorsement

eligible for selection as a case or control (for the nested case-control study) following their first prescription for HRT. Women stopped contributing person-time to the study on the earliest of the following: the date that endometrial cancer was diagnosed, the date of hysterectomy, the study end-date, or the date on which they left the practice. Age-specific incidence rates were calculated for each year after the initiation of HRT and age-adjusted incidence rate ratios (IRRs) were calculated for different categories of HRT exposure.

Classification of HRT Exposure in the Cohort Study

Four exposure categories were identified: (i) exposure to combined sequential HRT only (reference category); (ii) exposure to tibolone as first HRT product; (iii) exposure to continuous combined HRT as first HRT product; and (iv) exposure to tibolone after initial exposure to other HRT. The latter category was introduced to take account of the possibility that women with dysfunctional bleeding (commonly the first clinical presentation of endometrial cancer) whilst taking combined HRT were switched to tibolone (a bleed-free product) and diagnosed with endometrial cancer afterwards. With this pattern of prescribing it was expected that there would be differences in the incidence rates between exposure categories, with the higher rates in the early months after start of tibolone in category (iv). As an internal comparison, the same analysis was undertaken for continuous combined (i.e. bleed-free) HRT. Any person-time during or after tibolone exposure was disregarded for this part of the study.

For some women prescription data were recorded on the GPRD before the start of the study period. Consequently some women would be classified as 'tibolone starters' if it was their first HRT product after 1 January 1992 even though there was evidence that they had used other HRT products before 1992. Therefore exposure classification was carried out in two ways: (i) using strictly the HRT utilisation observed within the study period; and (ii) using all information on HRT utilisation available for the classification of exposure whilst still restricting person-time to the study period.

The age-adjusted IRRs for both methods of classifying exposure are presented. In the cohort analysis, duration of exposure was not taken into account: only person-time after initial exposure to HRT, tibolone, etc. was calculated. Person-time after initial exposure to combined sequential HRT was taken as the reference category. Person-time after exposure to tibolone counted towards tibolone-exposed person-time irrespective of subsequent switching to other products or discontinuation of treatment. Similarly, person-time after exposure to combined sequential HRT was attributed to the observed women-years exposed to combined sequential HRT, irrespective of discontinuation of use, or switching between products (with the exception of switching to tibolone).

Case Definition and Control Selection

Potential cases of endometrial cancer were identified through an automated search of all records with diagnostic codes for the disease. The records of all potential cases were reviewed and coded independently by three researchers to determine case status and event date. To be included, patients had to have a record of endometrial cancer plus evidence of treatment (e.g. hysterectomy, radiotherapy, medroxyprogesterone). We had no information on the histology of the cancer cases; consequently, the proportion of hormone-related endometrioid versus non-hormone-related, non-endometrioid (clear cell, serous) cancer could not be established. Cases of leiomyosarcoma, mullerian tumours and secondary endometrial carcinoma (e.g. ovarian or cervical tumours that had expanded to the endometrium) were excluded. Where there were differences between researchers in the classification of potential cases, the records were discussed in an attempt to reach a consensus. Where no consensus was reached, a gynaecological oncology specialist (Hilary Thomas) was consulted. A consensus was reached on all potential cases. During the entire process researchers were masked to HRT exposure.

Two sets of six controls were randomly selected for each case. The first set was matched on year of birth and the second on general practice. All controls had to be registered on the GPRD on the index date. At least 6 months of data had to be available on all study subjects (cases and controls) before the index date. Two different sets of controls were chosen for the following reason. In our opinion, we needed to match on age because of its potential for confounding and the chances that statistical adjustment for age might leave residual confounding. Matching on practice is debatable – some argue one should match on practice in an attempt to match on a proxy for socioeconomic status. Others argue that matching on practice may result in overmatching because one might be matching on prescribing behaviour. This would reduce the potential to identify any increase in risk. In our experience, in practice, this type of overmatching does not seem to be a problem (possibly because practices include many general practitioners (GPs) who have sufficiently different prescribing patterns). To be complete we decided to do both. Matching on age and general practice at the same time was impossible because it would have led to too many 'orphan cases' in the older age range, which might have distorted the results.

Potential Confounders

For all subjects we identified their BMI nearest to the date of diagnosis, smoking status, tamoxifen use and whether they had any of the following: hypertension, diabetes mellitus, gall bladder disease, early menopause, late menopause, polycystic ovary disease, presence of an estrogen-producing tumour, and presence of other cancers. Conditional logistic regression models were used to estimate crude and adjusted odds ratios (ORs) of endometrial cancer amongst tibolone users and users of continuous combined HRT, with users of sequential HRT only as the reference group. Criteria for consideration in the inclusion of variables in the model were $p < 0.20$ in the univariate analyses and $p < 0.05$ or significant contribution to the stability of the model in the multivariate analyses. We checked for interaction between variables. All statistical analyses were carried out using STATA version 7.0.[17]

Sensitivity Analyses

Compared with disorders such as infections, venous thromboembolism or fractures, cancer has a long lead time and it is the exposure at tumour initiation or tumour acceleration that we are interested in, not the exposure shortly before diagnosis. The lead time of endometrial cancer is unknown. It has been estimated to be anything between 1 year (from atypical hyperplasia to tumour diagnosis) and 15 years (from tumour initiation). Therefore, it is difficult to establish which exposure period is relevant although it is safe to say, for instance, that exposure on the day before diagnosis is irrelevant.

To investigate the possibility that women already had endometrial cancer when tibolone therapy was started, further analyses were undertaken in which the index date of endometrial cancer diagnosis was backdated by 6, 12, 18 and 24 months. Use of tibolone and combined HRT *before* the backdated index dates was then considered in relation to endometrial cancer risk. We selected new sets of controls on each of the backdated event dates; analyses were carried out as previously described.

Results

Cohort Study

For the study, 250 731 users of HRT aged 40–74 years were identified. The characteristics of all first-time HRT users are given in table I. 4995 women used tibolone as their first HRT product (2.0%); 10 783 (4.3%) of the users of combined HRT had changed to tibolone at some time during the study period.

Incidence Rate Ratios (IRRs) Based on Exposure Classification Only Considering HRT Use Within the Study Window

The age-adjusted IRR of endometrial cancer amongst women who had changed from combined HRT to tibolone, relative to those who continued

Table I. Population characteristics of first-time hormone replacement therapy users

Characteristic	No. of users (%)
Diabetes mellitus	2 755 (2.2)
Osteoporosis	4 593 (3.6)
Hypertension	13 030 (10.3)
Angina	2 481 (2.0)
Ischaemic heart disease	732 (0.6)
Hysterectomy:	
all	34 315 (27.0)
alone	22 162 (17.4)
with unilateral oophorectomy	3 792 (3.0)
with bilateral oophorectomy	8 361 (6.6)
BMI:	
≤19	4 049 (3.2)
20–24	26 902 (21.2)
25–29	15 737 (12.4)
30–34	5 327 (4.2)
35–39	1 499 (1.2)
40+	824 (0.6)
unknown	72 724 (57.2)
Smoking:	
smoker	20 957 (16.5)
ex-smoker	11 838 (9.3)
non-smoker	73 176 (57.6)
unknown	21 091 (16.6)
Alcohol consumption:	
non-drinker	21 667 (17.1)
light (1–9 units/week)	41 007 (32.3)
moderate (10–21 units/week)	3 532 (2.8)
heavy (22+ units/week)	770 (0.6)
unknown	60 086 (47.3)

BMI = body mass index.

taking combined sequential HRT, was 1.65 (95% CI 0.96, 2.83). Amongst women whose HRT began with tibolone the age-adjusted IRR relative to those who started with combined sequential HRT was 1.83 (95% CI 1.19, 2.82). Similar analyses were carried out for HRT consisting of continuous combined estrogen and progestogen products compared with sequential combined HRT. The age-adjusted incidence rate of endometrial cancer in women starting replacement therapy with continuous combined products was neutral compared with those starting sequential combined HRT (IRR 0.98; 95% CI 0.59, 1.62). For women who changed from sequential HRT to continuous combined HRT, the IRR was 1.36 (95% CI 0.82, 2.26).

IRRs Based on Exposure Classification Considering All HRT Use Before 1 March 1999

Using the second method of exposure classification, i.e. taking into account information on exposure prior to the study period, the age-adjusted IRR for endometrial cancer amongst women who had changed from combined HRT to tibolone was 1.88 (95% CI 1.18, 2.98) compared with women who continued taking combined sequential HRT. Amongst women whose replacement therapy began with tibolone, the age-adjusted IRR of endometrial cancer was 1.68 (95% CI 1.04, 2.71) compared with women starting combined sequential HRT. In the similar analysis of continuous combined HRT the IRR was 1.09 (95% CI 0.32, 1.87). For women who changed from combined sequential HRT to continuous combined HRT the IRR was 1.20 (95% CI 0.72, 1.98).

Nested Case-Control Study

The 162 cases of endometrial cancer were each matched to two sets of 972 controls. The distribution of risk factors between cases and controls with crude and adjusted ORs are presented in table II; increased ORs were found with increasing age and tamoxifen use (amongst the practice-matched set), whereas smoking was associated with a decreased OR.

Using index date of diagnosis as the reference point for determining the prior use of HRT, the adjusted OR of the risk of endometrial cancer in women who had ever used tibolone compared with the risk of endometrial cancer in users of combined sequential HRT was 1.58 (95% CI 1.01, 2.47). This estimate, based on cases that were practice-matched to controls, was similar to the corresponding estimate from age-matched analyses: 1.54 (95% CI 1.03, 2.32). In total, 43 women had been exposed to tibolone prior to their diagnosis of endometrial cancer.

To investigate the possibility that women had endometrial cancer when tibolone therapy was started, further analyses were undertaken in which the

Table II. Crude and adjusted odds ratios of risk factors for endometrial cancer in an hormone replacement therapy (HRT)-using population

Variable	No. of cases (n = 162)	Practice-matched controls			Age-matched controls		
		no. of controls (n = 972)	crude OR (95% CI)	adjusted OR (95% CI)	no. of controls (n = 972)	crude OR (95% CI)	adjusted OR (95% CI)
Early menopause	1	8	0.73 (0.08, 6.44)		2		
Endometriosis	0	5			7		
Prior cancer	4	14	1.71 (0.56, 5.21)		38	2.93 (1.60, 5.38)	2.85 (1.50, 5.46)
Hypertension	56	204	2.12 (1.45, 3.09)	1.53 (1.01, 2.31)	278	1.49 (1.04, 2.12)	1.52 (1.04, 2.21)
Thyroid disease	13	55	1.45 (0.78, 2.70)		71	1.11 (0.60, 2.06)	
High cholesterol	27	114	1.60 (0.98, 2.63)		123	1.38 (0.88, 2.18)	
Diabetes mellitus	3	15	1.20 (0.34, 4.22)		25	0.72 (0.22, 2.39)	
Gallbladder disease	9	60	0.90 (0.44, 1.83)		55	0.98 (0.47, 0.04)	
Tamoxifen	4	11	2.23 (0.70, 7.18)	4.24 (1.23, 14.59)	7	3.43 (1.00, 11.7)	3.00 (0.79, 11.43)
Mean age	58.8	54.2					
+1 year[a]			1.11 (1.08, 1.14)	1.10 (1.07, 1.13)			
BMI:							
<20	3	51	0.45 (0.14, 1.50)	0.41 (0.12, 1.45)	35	0.59 (0.18, 1.99)	0.59 (0.17, 2.09)
20 to <25	55	431	Reference	Reference	389	Reference	Reference
25 to <30	50	246	1.60 (1.06, 2.42)	1.50 (0.97, 2.31)	293	1.21 (0.80, 1.83)	1.18 (0.77, 1.82)
30 to <35	16	80	1.59 (0.87, 2.91)	1.29 (0.68, 2.48)	111	1.01 (0.56, 1.84)	0.95 (0.51, 1.76)
>35	6	20	2.35 (0.90, 6.14)	2.10 (0.75, 5.87)	18	2.35 (0.90, 6.13)	2.18 (0.80, 5.90)
unknown	32	144	1.81 (1.10, 3.00)	2.21 (1.23, 3.98)	126	1.84 (1.13, 2.98)	2.07 (1.17, 3.64)
Smoking:							
non-smoker	129	644	Reference	Reference	652	Reference	Reference
smoker	19	262	0.36 (0.21, 0.59)	0.44 (0.26, 0.75)	252	0.38 (0.23, 0.63)	0.37 (0.22, 0.62)
smoking unknown	14	66	1.07 (0.57, 2.00)	0.78 (0.37, 1.65)	68	1.04 (0.57, 1.92)	0.71 (0.34, 1.47)
HRT before index date:							
combined sequential	131	849	0.60 (0.38, 0.94)		777	1.06 (0.69, 1.65)	
estrogen only	27	158	1.03 (0.66, 1.62)		187	0.84 (0.53, 1.31)	
continuous combined	5	23	1.38 (0.47, 4.08)		34	0.87 (0.32, 2.36)	
tibolone	43	122	2.36 (1.54, 3.64)	1.58 (1.01, 2.47)	182	1.61 (1.08, 2.39)	1.54 (1.03, 2.32)

a Reflects the odds ratio associated with each year of increase in age.

BMI = body mass index; **OR** = odds ratio.

index date of endometrial cancer diagnosis was backdated by 6, 12, 18 and 24 months. The use of tibolone and combined HRT *before* the backdated index dates was then considered in relation to endometrial cancer risk. The adjusted OR increased with increasing backdating, but confidence intervals overlapped and point estimates became less stable as backdating increased (table III). The adjusted OR also increased with the duration of tibolone use, with confidence interval overlapping: from 1.13 (95% CI 0.50, 2.51) for tibolone use of <3 months to 2.01 (95% CI 1.02, 3.96) for use of >24 months in the age-matched analyses, and from 1.31 (95% CI 0.58, 2.95) to 4.10 (95% CI 1.94, 8.66) for the same durations in the practice-matched analyses.

Discussion

Women treated with tibolone for at least 2 years were more likely to develop endometrial carcinoma than users of other HRT products. Continuous combined estrogen and progestogen use was associated with a 47% reduction in risk. The latter is consistent with findings in clinical studies suggesting a decreased risk in women using continuous combined HRT.[18] Studies of endometrial toxicity of combined sequential HRT show conflicting results,[19] with some demonstrating an increase in risk[20,21] and others, including one on the same database,[22] showing a decrease or giving neutral risk estimates.[23]

Tibolone is licensed for use in women who have not experienced vaginal bleeding for at least 12 months. Nonetheless, it is possible that tibolone has been prescribed preferentially to women experiencing bleeding on other HRT products. Anecdotally, we did find that some tibolone was prescribed to women with clear histories of dysfunctional uterine bleeding. However, we have not investigated its extent nor compared the frequency of dysfunctional uterine bleeding amongst women starting different types of HRT. In our cohort study, we tried to overcome this potential problem by distinguishing between those who switched to tibolone from other HRT and those who used tibolone as their first HRT product, to take account of the possibility that women who experienced dysfunctional bleeding whilst taking combined sequential HRT were switched to tibolone and diagnosed with endometrial cancer afterwards. With this prescribing pattern, it was expected that there would be differences in the incidence rates, with the higher rates in the early months after start of tibolone in those who switched to tibolone. We could not demonstrate any such patterns. However, there were only 43 tibolone-exposed patients, 28 of whom had used other HRT before or after tibolone. Consequently, the data are fragile.

In the case-control study, to investigate the possibility that women had endometrial cancer when tibolone therapy was started, further analyses were undertaken in which the index date of endometrial cancer diagnosis was backdated by 6, 12, 18 and 24 months. Use of tibolone and combined HRT prior to the backdated index dates was then considered in relation to endometrial cancer risk. The point estimates for the ORs increased with backdating; confidence intervals overlapped and point estimates became less stable as a result of decreasing numbers of cases for which data were available.

This raises two questions:

- What is the interval between the first occurrence of spotting or dysfunctional bleeding and diagnosis?

Table III. Odds ratios (ORs) of tibolone and endometrial cancer with backdated index dates[a]

Backdated period	Adjusted OR (age matched)	Adjusted OR (practice matched)
Index date	1.54 (1.03, 2.32)	1.58 (1.01, 2.47)
Index date – 6 months	1.57 (1.03, 2.38)	1.80 (1.12, 2.89)
Index date – 12 months	1.98 (1.29, 3.05)	2.49 (1.55, 4.03)
Index date – 18 months	2.74 (1.79, 4.22)	2.64 (1.62, 4.30)
Index date – 24 months	2.65 (1.71, 4.09)	3.27 (1.94, 5.50)

a ORs increased with backdating the event date, χ^2 test for trend, $p < 0.05$.

- What is the interval between the occurrence of spotting or dysfunctional bleeding and the woman consulting a doctor (who may then prescribe a bleed-free HRT product)?

If there is a 6-month period between the occurrence of the first symptoms of hyperplasia or endometrial cancer and the woman visiting her GP and then there are another 18 months between this visit and further visits eventually leading to an endometrial cancer diagnosis, then backdating by 2 years will be insufficient to resolve this issue. However, we did not have enough data to backdate the event date further.

The biological plausibility of our results is questionable. Most known risk factors are associated with excess estrogen and the present findings raise the question whether the estrogenic properties of tibolone are sufficiently opposed by its progestogenic activity. Other than a case series[1] and one case report,[24] we are unaware of any earlier epidemiological studies suggesting an increased risk of endometrial hyperplasia or carcinoma associated with tibolone. Clinical studies comparing effects on the endometrium of tibolone with other HRT suggest significantly less bleeding and spotting, but similar endometrial thickening or atrophy.[9,12,25] However, endometrial thickening is only a surrogate marker. Each of the studies involved fewer than 200 patients and did not have the power to detect an increased risk of endometrial cancer.

Tibolone is metabolised locally by 3β-hydroxysteroid dehydrogenase/isomerase and the metabolites in the endometrium have no estrogenic activity.[8] Little is known about the prevalence of deficiencies of this enzyme; such deficiencies might explain the findings from this investigation. In addition, tibolone has been shown *in vivo* to be metabolised to a strong estrogenic metabolite: 7-α-methyl-ethinyl estradiol, which is able to stimulate the endometrium, though maybe only if there is reduced progestogenic activity of tibolone.[26,27] This might be the case in some patients with reduced local enzyme activity for the production of the progestogenic metabolite.

Conclusions

Our data are fragile and follow-up time is insufficient to draw any firm conclusions with respect to the endometrial safety of tibolone: a study should be carried out on a larger number of cases drawn from an HRT-using population, for whom more follow-up data are available. Ideally, this should include a population that is large enough to distinguish users of one HRT product only, i.e. those only ever exposed to tibolone versus those only ever exposed to combined HRT.

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The study was overseen by an independent scientific advisory board comprising experts in gynaecological oncology, pathology, (pharmaco)epidemiology and statistics and the study was carried out in accordance with their recommendations. The funding organisation was not present at the meetings of the scientific advisory board and had no say in the way in which the study was carried out. The research contract was unconditional and the authors have the right to publish without consulting the funding organisation.

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