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Endometrial Hyperplasia Risk in Relation to Recent Use of Oral Contraceptives and Hormone Therapy

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Abstract

Purpose—Examine the relationship between recent use of oral contraceptives and hormone therapy and endometrial hyperplasia (EH) risk.

Methods—Cases comprised women diagnosed with complex EH (n=289) or atypical EH (n=173) between 1985–2003. One age-matched control was selected for each case; excluded were women with a prior hysterectomy or diagnosis of EH or endometrial cancer. Hormone use in the six months prior to the date of the case's first symptoms was ascertained using a pharmacy database and medical records. Odds ratios (OR) and 95% confidence intervals (CI) were calculated.

Results—Three (1.1%) cases had used oral contraceptives, compared to sixteen (6.0%) controls (OR = 0.2, 95% CI: 0.0–0.6). Fifty-one (16.8%) cases had taken estrogen-only hormone therapy, in contrast to two (0.7%) controls (OR = 37.6, 95% CI: 8.8–160.0). The risk of EH among estrogen plus progestin hormone users did not differ from that of non-users (OR = 0.7, 95% CI: 0.4–1.1).

Conclusions—This study suggests that previous findings of the association of estrogen-only hormone therapy with increased risk of EH and the lack of an association between estrogen plus progestin hormone therapy and EH risk are likely to apply to both complex EH and atypical EH. Further examination of the association between oral contraceptives and EH, with greater numbers of OC users, is warranted.

Keywords

endometrial hyperplasia; oral contraceptives; hormone therapy; exogenous hormones

Introduction

Endometrial hyperplasia (EH) is a precancerous, noninvasive proliferation of the lining of the uterus. Classification of EH is done in two ways: based on architectural crowding as simple versus complex (with back-to-back glandular crowding in the case of complex hyperplasia); and based on nuclear irregularity, defined as with or without cytologic atypia (1–3). Rarely progressing to cancer, simple hyperplasia often spontaneously regresses, whereas complex

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hyperplasia and hyperplasia with atypia, the less common types, are more likely to progress to cancer and so are commonly treated with a progestin or hysterectomy (1,4-10).

Known risk factors for the occurrence of EH are related to an imbalance of excess estrogen as compared to progesterone, resulting in the stimulation of endometrial cell growth (11,12). For example, a strong positive association of estrogen-only post-menopausal hormone therapy with EH has been demonstrated in numerous studies (13-16). As this strong association with estrogen-only hormone therapy has also been seen with endometrial cancer, many studies, including 48 randomized trials, have examined the effect of combined estrogen and progestin postmenopausal hormone therapy on the development of endometrial pathology (15). Few of these studies, however, have distinguished among the specific types of hyperplasia, for which controversy exists as to their potentially varying etiologies, and even fewer studies have examined the relationship between contraceptive hormone use and risk of EH (13,16-20). The two case-control studies that did analyze the relationship between oral contraceptives and incidence of EH did not find an association, but were limited by self-report of medication use and did not examine recent use specifically (21,22).

The present case-control study was conducted to examine the relationship between recent use of combined estrogen and progestin oral contraceptives (OCs), estrogen-only hormone therapy (ET), and combined estrogen plus progestin hormone therapy (EPT) and risk of complex EH and EH with atypia.

Methods

The study population and data collection methods for this study have been described elsewhere (Epplein et al., submitted for publication, 2007); a brief description follows.

The setting was Group Health (GH), a Washington state integrated health plan with over 500,000 enrollees. Cases included all female members of GH, over the age of 18 years, who were diagnosed with possible complex EH or possible EH with atypia between January 1, 1985 and December 31, 2003. Potential cases were excluded if they had a previous diagnosis of endometrial cancer. Because of the known ambiguities in the diagnosis of EH, study cases were also required to have a diagnosis of complex hyperplasia or hyperplasia with atypia assigned in a separate review. Specifically, all pathology slides from the potential cases identified through GH pathology text searches were independently reviewed by two outside pathologists, utilizing standardized diagnostic criteria. When the two pathologists disagreed (22.2 percent of the time), the slides were read by a third pathologist. If the third pathologist disagreed with both of the initial diagnoses, the diagnosis was assigned by the senior pathologist.

Controls were selected randomly from the membership files of GH from 1985–2003, excluding women who had a prior hysterectomy or who had a previous diagnosis of EH or endometrial cancer. One control was selected for each case. Controls were matched to cases by year of birth (+/- one year) and were required to have been enrolled at GH at the time of the case's diagnosis of EH. To ensure that the controls actually used GH as their primary care institution, we sought to choose as controls women who had received GH services (i.e., seen a medical professional there, whether for a well-adult visit or any other reason) at least once in the three years prior to the time their matched case was diagnosed.

The Group Health automated pharmacy database provided information on oral contraceptives and post-menopausal hormones dispensed to study subjects. It contains data on all prescriptions for medications dispensed to enrollees through GH pharmacies since 1977. The data included the specific drug and drug class, date and amount dispensed, and dosing instructions, where available. For each case and her matched control, hormonal medications dispensed were

examined prior to the one month before the case's onset of abnormal vaginal bleeding ("reference date"). For those missing information on abnormal bleeding (n=72), the reference date was assigned as three months prior to the biopsy date (the median duration of abnormal bleeding among the cases).

Trained medical abstractors obtained the following variables of interest from the paper and electronic medical records of cases and controls: parity (defined as the number of pregnancies of at least 20 weeks gestation); race; smoking status at reference date; medical history, including a diagnosis of diabetes or hypertension (presence of elevated or high blood pressure that was treated with medications or lifestyle changes); height and weight (kg/m²) as of the reference date; and a previous weight, at least one year prior to that time.

The Group Health Enrollment database was queried to determine dates of enrollment for each study subject, and residential zip code at reference date (or the closest time thereof). Study subjects' zip codes were then used to find the median income in their geographical region, as determined by the 1990 US Census (Summary Tape File 3). Median income was not available for zip code areas where the population was deemed too small by the US Census Bureau, so as to abide by confidentiality laws, resulting in missing information on residential median income for 19 (4.1%) cases and 23 (5.0%) controls.

Of the 548 women with diagnoses of complex EH (n=332) or EH with atypia (n=216), 40 were excluded because of missing medical charts. Also excluded were 19 controls and 30 cases, and their matched counterparts, who were not enrolled at GH for at least 6 months prior to the reference date (and thus lacked sufficient pharmacy data for analysis), and one case and her matched control whose onset of symptoms was 8 years prior to diagnosis, resulting in a total of 462 cases (289 complex and 173 atypia) and 462 controls. While we would have preferred to investigate hormone use in the two (or even three) years prior to the reference date, rather than limiting our analyses to only the prior 6 months, we found that 26% of our subjects (or their matched counterparts) were not enrolled for at least two years prior to the reference date, and thus would have had to been dropped from our analyses.

Data analysis

The data analysis was performed with the goal of determining the association between complex EH and EH with atypia and the following exposures: combined estrogen and progestin oral contraceptive (OC), estrogen-only post-menopausal hormone therapy (ET), and combined estrogen plus progestin post-menopausal hormone therapy (EPT). OC users were defined as women who were dispensed one of these preparations for more than 1 month. ET users were defined as women who were dispensed ET for 60 days or more. For EPT, users were defined as women who were dispensed estrogen for 60 days or more and progestin for 20 days or more during the same time period. Women who had been dispensed both estrogen and progestin within the 6 months prior to the reference date but whose total number of days of intended progestin use was less than one-third of their total number of days of intended estrogen use (16 cases of complex hyperplasia, 11 cases of hyperplasia with atypia, and 6 controls) were excluded from the analyses. The rationale for this exclusion was that we were not able to determine whether these women were ET users who then took progestin, or EPT users who took a smaller amount of progestin than the 10 days per month generally recommended. The comparison group for each of these analyses consisted of women who were prescribed no exogenous hormones.

The variables age, race, zip code (as a proxy for socioeconomic factors), years enrolled in GH, body mass index, parity, diabetes, hypertension, and smoking were evaluated as potential confounders. The decision was made a priori to include in the models only those variables that were shown in the data to be related both to the exposure of interest and the outcome of EH.

We used conditional logistic regression (23) to test the association of exogenous hormones with: 1) complex hyperplasia, 2) hyperplasia with atypia, and 3) either complex or atypical hyperplasia. Results are presented as odds ratios with 95% confidence intervals.

All analyses were performed with the STATA version 8.0 software package (College Station, Texas). To determine an upper confidence interval in the case of an odds ratio of 0.0, we used the PAIRS software within PEPI, version 4.0 (Salt Lake City, Utah).

Results

Women with complex EH or hyperplasia with atypia were similar to their matched controls in terms of age, race, median income of residential zip code area, and years enrolled in Group Health. As expected, cases were more likely than controls to be obese or morbidly obese, to never have given birth, to never have smoked, and to be diabetic (Table 1). However, only body mass index was adjusted for in the main analyses as it was the only covariate shown in the data to be related both to the exposures of interest and the outcome of EH.

Only three (1.1%) women with EH had been dispensed oral contraceptives in the 6 months prior to their onset of abnormal bleeding, while sixteen (6.0%) controls had been dispensed OCs in the 6 months before the bleeding onset date of their matched cases (OR=0.2, 95% CI: 0.0-0.6, adjusted for body mass index). There was a suggestion that oral contraceptive use was associated with a decreased risk of both complex hyperplasia and hyperplasia with atypia, but the numbers were small and the confidence intervals included one (Table 2). We also sought to assess the relationship between use of OCs for at least one year among the smaller subset of cases and controls who were enrolled for at least two years prior to the onset of symptoms, however this caused the confidence intervals around our estimates of relative risk to widen considerably (data not shown).

Fifty-one (16.8%) of the women with EH had been dispensed estrogen-only hormone therapy in the 6 months prior to the onset of abnormal bleeding, in contrast to two (0.7%) of the controls. Adjusting for body-mass index, such use was associated with a 37-fold increase in risk (OR=37.6, 95% CI: 8.8-160.0). A large increase in risk persisted for both complex hyperplasia and hyperplasia with atypia when analyzed separately (OR=51.3, 95% CI: 6.8-390.1; and OR=22.7, 95% CI: 2.8-181.3, respectively) (Table 2).

The risk of either complex hyperplasia or hyperplasia with atypia among combined estrogen plus progestin postmenopausal hormone users in the 6 months prior to the onset of abnormal bleeding did not substantially differ from that of non-hormone-users (OR=0.8, 95% CI: 0.4-1.4; and OR=0.6, 95% CI: 0.3-1.3, respectively) (Table 2). Furthermore, the risk of complex EH or EH with atypia did not vary by duration (within the 2-3 years prior to the reference date) of combined EPT use when progestin was taken at least 10 days a month (data not shown).

Discussion

By utilizing the Group Health automated pharmacy database, this study was able to ascertain almost all prescription fills of recent post-menopausal hormone therapy by study subjects, as a telephone survey conducted in the 1990s found that 97% of female respondents replied that they exclusively used GH pharmacies for their post-menopausal hormone prescriptions (24). However, we do not know what percentage of study subjects might have used non-GH pharmacies for their oral contraceptive prescriptions. Additionally, there are several features of the information we obtained from this database which present limitations for this study. Our inability to investigate hormone use for all subjects prior to the 6 months before the reference date allows for the possibility of confounding by prior use. As we did not directly interview our subjects, we had to assign "start dates" and "end dates" when a woman picked up a new

prescription that overlapped with the previous prescription. Dosage instructions were not always present, therefore we used number dispensed to determine days of use when assessing the impact of hormone therapy on EH. Lastly, we were unable to assess compliance for any medications, although in an unpublished study of similar women it was found that 95% of women indicated that they did indeed use the drugs that were dispensed to them from GH pharmacies.

The possibility of misclassification also exists in that by examining recent hormone use only, it might be argued that we have not obtained exposure information for the relevant time period. However, the endometrium is a very dynamic tissue and proliferative states as well as apoptotic states are induced within 14 days with hormonal stimulation within a single menstrual cycle, (25) indicating that examination of recency of use in the 6 months prior to onset of symptoms is appropriate for a study of endometrial hyperplasia.

Another limitation is that women taking postmenopausal hormones or oral contraceptives are likely to be seen more regularly by their prescribing physician (generally a gynecologist, but also possibly a family practice doctor or internist) than hormone nonusers, and thus might be more likely to receive an endometrial biopsy to evaluate abnormal bleeding. In this way, a relatively higher proportion of oral contraceptive and hormone therapy users with EH might have their condition recognized. This would be expected to produce an upward bias in the odds ratio relating use of any of these medications to the incidence of EH.

Also of concern in studying these potential associations is whether the prescription for hormonal therapy or OCs precedes the initial symptoms of EH. In this study we were able to ascertain the date the first symptoms of EH reportedly began on 71% of cases. We then examined medication use only prior to that date. When we did not have this date, we assigned a reference date of 3 months prior to the biopsy date (the median duration of time of abnormal bleeding prior to biopsy among cases with that information). We also excluded any prescriptions filled in the one month prior to the reference date. However, this does not exclude the possibility of some hormonal therapy following the onset of hyperplasia, such as if abnormal bleeding is not reported when it is actually present or if a woman has EH but no abnormal bleeding. This would result in a downward bias in the associations between hormonal therapies and EH.

Finally, it is possible that some of our controls may have undiagnosed complex EH or EH with atypia. However, even if this were so, it would most likely result in a very modest number of cases being misclassified as controls, as a recent study of endometrial biopsies of almost 3,000 women found that less than 1% of asymptomatic peri- and post-menopausal women had previously undetected EH (26). Selecting a control group of women who had undergone biopsies but were not found to have EH would not be an acceptable alternative as they would not be expected to have hormone medication histories that would be representative of the general population from whence the cases arose.

The present study found a strong reduction in risk of EH among recent users of oral contraceptives (OR=0.2, 95% CI: 0.0–0.6). Previous case-control studies, which addressed lifetime oral contraceptive use, and not necessarily recent use, failed to observe an association (21,22). However, studies of the association of combined OCs with endometrial cancer have consistently found a reduction in risk among users, with the reduction in risk beginning as early as the first year of use (27–29). Since the discontinuation in the United States of sequential OCs in 1976 due to their association with both EH and unwanted pregnancies, current OCs include low doses of estrogen combined with a variety of progestins. The low-dose OCs in use today are progestin dominant and are known to inhibit the proliferative changes that occur in the normal cycling endometrium (30–34). Further epidemiologic studies that focus on the

bioequivalence and doses of progestins in OC formulations and their relationship to complex and atypical hyperplasia would be of benefit.

In this study we observed a very strong association, albeit with rather wide confidence intervals, of recent estrogen-only hormone therapy use and complex EH or EH with atypia (OR=37.6, 95% CI: 8.8–160.0), even after adjustment for body mass index. That such an association exists is unsurprising, given that estrogen stimulates endometrial proliferation by binding to receptors in the nuclei of endometrial cells (30). And indeed, the association between ET and hyperplasia has been well established in the literature in randomized trials of post-menopausal hormone therapy (13-16). The association between ET and endometrial cancer has also been well-documented (27,35,36). The one case-control study of the etiology of EH that examined ET use found that among post-menopausal women, use of unopposed estrogens for 1-60 months was associated with an odds ratio of 3.1 (95% CI: 1.3-7.5), and use for greater than 60 months was associated with an odds ratio of 20.6 (5.8-72.5), all adjusted for body mass index (21). Recency of use was not specifically addressed in that study.

We observed the risk of EH to be similar among hormone non-users and women who, in the 6 months prior to the reference date, took EPT. The lack of association also held when analyzing combined EPT in the 2 or 3 years prior to the reference date (data not shown). Recent randomized trials have found no difference in risk of hyperplasia between women who took EPT with continuous or at least 12 days per month of progestin use and women who took a placebo (13-15,37-39). In a review of 18 randomized trials published in 2000, continuous EPT was not associated with hyperplasia incidence, while sequential estrogen plus progestin therapy did appear to increase risk (16). It is important to note here that for the majority of the studies in this review, however, hyperplasia of all types was the outcome of interest, including simple hyperplasia, the most common type of EH and the one most likely to spontaneously regress (1,4,13,40). The findings in the present study are also similar to those found in most studies of endometrial cancer, in which EPT regimens where progestin was given for 10 days or more did not increase endometrial cancer risk (39,41,42).

The present study suggests that previous findings of the association of estrogen-only hormone therapy with increased risk of EH and the lack of an association between estrogen plus progestin hormone therapy and EH risk are likely to apply specifically both to complex EH and to EH with atypia. The study's observation of a substantial reduction in risk of these forms of hyperplasia associated with recent use of OCs is not surprising, given the likely protection that such use affords against endometrial cancer. Nonetheless this association has not been thoroughly explored previously, and future studies, with larger datasets including greater numbers of OC users for more stable estimates, are needed to analyze this relationship.

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List of abbreviations

EH, endometrial hyperplasia; OR, odds ratio; CI, confidence interval; OCs, combined estrogen and progestin oral contraceptives; ET, estrogen-only hormone therapy; EPT, combined estrogen plus progestin hormone therapy; GH, Group Health of Seattle, Washington.

References

1. Kurman RJ, Kaminski PF, Norris HJ. The behavior of endometrial hyperplasia: A long-term study of 'untreated' hyperplasia in 170 patients. *Cancer* 1985;56:403–412. [PubMed: 4005805]

2. Kurman, RJ., editor. Blaustein's pathology of the female genital tract. Springer-Verlag; New York: 1994.
3. Silverberg, SG.; Kurman, RJ.; Nogales, F.; Mutter, GL.; Kubik-Huch, RA.; Tavassoli, FA. Tumours of the uterine corpus: Epithelial tumours and related lesions. In: Tavassoli, FA.; Devilee, P., editors. Pathology & Genetics: Tumours of the Breast and Female Genital Organs. IARCPress; Lyon: 2003. p. 221-232.
4. Ferenczy A, Gelfand M. The biologic significance of cytologic atypia in progestogen-treated endometrial hyperplasia. *Am J Obstet Gynecol* 1989;160:126–131. [PubMed: 2912075]
5. Kurman RJ, Felix JC, Archer DF, Nanavati N, Arce J-C, Moyer DL. Norethindrone acetate and estradiol-Induced endometrial hyperplasia. *Obstet Gynecol* 2000;96(3):373–379. [PubMed: 10960628]
6. Lindahl B, Willen R. Spontaneous endometrial hyperplasia: a prospective, 5 year follow-up of 246 patients after abrasio only, including 380 patients followed-up for 2 years. *Anticancer Res* 1994;14:2141–2146. [PubMed: 7840513]
7. Hunter JE, Tritz DE, Howell MG, DePriest PD, Gallion HH, Andrews SJ, et al. The prognostic and therapeutic implications of cytologic atypia in patients with endometrial hyperplasia. *Gynecol Oncol* 1994;55:66–71. [PubMed: 7959270]
8. Hammond R, Johnson J. Endometrial hyperplasia. *Curr Obstet Gynecol* 2004;14:99–103.
9. Horn LC, Schnurbusch U, Bilek K, Hentschel B, Einkenkel J. Risk of progression in complex and atypical endometrial hyperplasia: clinicopathologic analysis in cases with and without progestogen treatment. *Int J Gynecol Cancer* 2004;14(2):348–353. [PubMed: 15086736]
10. Lacey JV, Ioffe OB, Ronnett BM, Rush BB, Richesson DA, Chatterjee N, et al. Endometrial carcinoma risk among women diagnosed with endometrial hyperplasia: the 34-year experience in a large health plan. *Br J Cancer* 2008;98(1):45–53. [PubMed: 18026193]
11. Anderson JN, Peck EJJ, Clark JH. Estrogen-induced uterine responses and growth: relationship to receptor estrogen binding by uterine nuclei. *Endocrinology* 1975;96:160–7. [PubMed: 162876]
12. Gusberg SB. Hormone-dependence of endometrial cancer. *Obstet Gynecol* 1967;30:287–93. [PubMed: 5212339]
13. The Writing Group for the PEPI Trial. Effects of hormone replacement therapy on endometrial histology in postmenopausal women: The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* 1996;275:370–375. [PubMed: 8569016]
14. Speroff L, Rowan J, Symons J, Genant H, Wilborn W. The Comparative Effect on Bone Density, Endometrium, and Lipids of Continuous Hormones as Replacement Therapy (CHART Study): A Randomized Controlled Trial. *JAMA* 1996;276:1397–1403. [PubMed: 8892714]
15. Pickar JH, Thorneycroft I, Whitehead M. Effects of hormone replacement therapy on the endometrium and lipid parameters: A review of randomized clinical trials, 1985 to 1995. *Am J Obstet Gynecol* 1998;178:1087–1099. [PubMed: 9609589]
16. Lethaby A, Farquhar C, Sarkis A, Roberts H, Jepson R, Barlow D. Hormone replacement therapy in postmenopausal women: Endometrial hyperplasia and irregular bleeding. *Cochrane Database Syst Rev* 2000;2:CD000402. [PubMed: 10796715]
17. Bergeron C, Fox H. Low incidence of endometrial hyperplasia with acceptable bleeding patterns in women taking sequential hormone replacement therapy with dydrogesterone. *Gynecol Endocrinol* 2000;14(4):275–281. [PubMed: 11075299]
18. Hill DA, Weiss NS, Beresford SA, Voigt LF, Daling JR, Stanford JL, et al. Continuous combined hormone replacement therapy and risk of endometrial cancer. *Am J Obstet Gynecol* 2000;183:1456–1461. [PubMed: 11120510]
19. Wiedepass E, Adami H-O, Baron JA, Magnusson C, Bergstrom R, Lindgren A, et al. Risk of endometrial cancer following estrogen replacement with and without progestins. *J Natl Cancer Inst* 1999;91(13):1131–1137. [PubMed: 10393721]
20. Wells M, Sturdee DW, Barlow DH, Ulrich LG, O'Brien K, Campbell MJ, et al. Effect on endometrium of long term treatment with continuous combined oestrogen-progestogen replacement therapy: follow up study. *Br Med J* 2002;325(7358):239–243. [PubMed: 12153918]

21. Kreiger N, Marrett LD, Clarke EA, Hilditch S, Woolever CA. Risk factors for adenomatous endometrial hyperplasia: a case-control study. *Am J Epidemiol* 1986;123(2):291–300. [PubMed: 3946378]
22. Ricci E, Moroni S, Parazzini F, Surace M, Benzi G, Salerio B, et al. Risk factors for endometrial hyperplasia: results from a case-control study. *Int J Gynecol Cancer* 2002;12:257–260. [PubMed: 12060446]
23. Breslow, NE.; Day, NE. *Statistical Methods in Cancer Research, Volume I: The Analysis of Case-Control Studies*. IARC Scientific Publications; Lyon: 1980.
24. Psaty BM, Heckbert SR, Atkins D, Lemaitre R, Koepsell TD, Wahl PW, et al. The risk of myocardial infarction associated with the combined use of estrogens and progestins in postmenopausal women. *Arch Intern Med* 1994;154:1333–1339. [PubMed: 8002685]
25. Whitehead MI, Townsend PT, Pryse-Davies J, Ryder TA, King RJ. Effects of estrogens and progestins on the biochemistry and morphology of the postmenopausal endometrium. *NEJM* 1981;305(27):1599–1605. [PubMed: 7312007]
26. Korhonen MO, Symons JP, Hyde BM, Rowan JP, Wilborn WH. Histologic classification and pathologic findings for endometrial biopsy specimens obtained from 2964 perimenopausal and postmenopausal women undergoing screening for continuous hormones as replacement therapy (CHART 2 Study). *Am J Obstet Gynecol* 1997;176(2):377–380. [PubMed: 9065185]
27. Cook, LS.; Weiss, NS.; Doherty, JA.; Chen, C. Endometrial Cancer. In: Schottenfeld, D.; Fraumeni, J.; J., F., editors. *Cancer Epidemiology and Prevention*. Third. Oxford University Press; Oxford: 2006. p. 1027-1043.
28. Drife J. Benefits and risks of oral contraceptives. *Adv Contracept* 1990;6(suppl):15–25. [PubMed: 2291444]
29. Kaufman DW, Shapiro S, Slone D, Rosenberg L, Miettinen OS, Stolley PD, et al. Decreased risk of endometrial cancer among oral-contraceptive users. *N Engl J Med* 1980;303:1045–1047. [PubMed: 7421893]
30. Deligdisch L. Hormonal pathology of the endometrium. *Mod Pathol* 2000;13(3):285–294. [PubMed: 10757339]
31. Anderson FD, Feldman R, Reape KZ. Endometrial effects of a 91-day extended-regimen oral contraceptive with low-dose estrogen in place of placebo. *Contraception* 2008;77(2):91–96. [PubMed: 18226671]
32. Archer DF. Endometrial histology during use of a low-dose estrogen-desogestrel oral contraceptive with a reduced hormone-free interval. *Contraception* 1999;60(3):151–154. [PubMed: 10640158]
33. Coenen CM, Hollanders JM, Rolland R, Spielmann D, Bulten J. The effects of a low-dose gestodene-containing oral contraceptive on endometrial histology in healthy women. *Eur J Contracept Reprod Health Care* 1996;1:325–329. [PubMed: 9678115]
34. Johnson JV, Grubb GS, Constantine CD. Endometrial histology following 1 year of a continuous daily regimen of levonorgestrel 90 mcg/ethinyl estradiol 20 mcg. *Contraception* 2007;75:23–26. [PubMed: 17161119]
35. Herrington LJ, Weiss NS. Postmenopausal unopposed estrogens: characteristics of use in relation to risk of endometrial carcinoma. *Ann Epidemiol* 1993;3:308–318.
36. Grady D, Gebretsadik T, Kerlikowske K, Ernster V, Petitti D. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. *Obstet Gynecol* 1995;85:304–313. [PubMed: 7824251]
37. Pickar JH, Yeh I-T, Wheeler JE, Cunnane MF, Speroff L. Endometrial effects of lower doses of conjugated equine estrogens and medroxyprogesterone acetate. *Fertil Steril* 2001;76(1):25–31. [PubMed: 11438315]
38. Brynhildsen J, Hammar M. Low dose transdermal estradiol/norethisterone acetate treatment over 2 years does not cause endometrial proliferation in postmenopausal women. *Menopause* 2002;9:137–144. [PubMed: 11875333]
39. Anderson GL, Judd HL, Kaunitz AM, Barad DH, Beresford SA, Pettinger M, et al. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures. *JAMA* 2003;290:1739–1748. [PubMed: 14519708]

40. Terakawa N, Kigawa J, Taketani Y, Yoshikawa H, Yajima A, Noda K, et al. The behavior of endometrial hyperplasia: A prospective study. *J Obstet Gynaecol Res* 1997;23(3):223–230. [PubMed: 9255033]
41. Voigt LF, Weiss NS, Chu J, Daling JR, McKnight B, Van Belle G. Progestagen supplementation of exogenous oestrogens and risk of endometrial cancer. *Lancet* 1991;338:274–277. [PubMed: 1677110]
42. Pike MC, Peters RK, Cozen W, Probst-Hensch NM, Felix JC, Wan PC, et al. Estrogenprogestin replacement therapy and endometrial cancer. *J Natl Cancer Inst* 1997;89:1110–1116. [PubMed: 9262248]

Table 1

Selected characteristics of cases and controls

	Complex Hyperplasia Cases (n=268) n (%)	Matched Controls (n=268) n (%)	Atypical Hyperplasia Cases (n=162) n (%)	Matched Controls(n=162)n (%)
Age at reference date (years)				
<45	61 (22.8)	57 (21.3)	21 (13.0)	21 (13.0)
45-54	89 (33.2)	94 (35.1)	53 (32.7)	53 (32.7)
55-64	51 (19.0)	50 (18.7)	40 (24.7)	40 (24.7)
65+*	67 (25.0)	67 (25.0)	48 (29.6)	48 (29.6)
Race*				
Non-Hispanic White	234 (88.6)	242 (90.6)	150 (92.6)	142 (87.7)
Asian	18 (6.8)	12 (4.5)	8 (4.9)	10 (6.2)
African American	6 (2.3)	10 (3.8)	2 (1.2)	5 (3.1)
Other	6 (2.3)	3 (1.1)	2 (1.2)	5 (3.1)
Median income of residential zip code area**				
<\$30,000	63 (24.9)	58 (22.8)	28 (17.7)	27 (17.7)
\$30,000-\$40,000	115 (45.5)	139 (54.7)	81 (51.3)	79 (51.6)
>\$40,000	75 (29.6)	57 (22.4)	49 (31.0)	47 (30.7)
Years Enrolled in GH				
<5	56 (20.9)	52 (19.4)	25 (15.4)	29 (17.9)
5-9	76 (28.4)	97 (36.2)	30 (18.5)	39 (24.1)
10-14	72 (26.9)	62 (23.1)	44 (27.2)	47 (29.0)
15+	64 (23.9)	57 (21.3)	63 (38.9)	47 (29.0)
Body mass index (kg/m ²)†				
Not overweight (<24.9)	78 (29.3)	138 (51.7)	46 (28.4)	70 (43.8)
Overweight (25–29.9)	63 (23.7)	66 (24.7)	33 (20.4)	45 (28.1)
Obese (30–39.9)	77 (29.0)	55 (20.6)	49 (30.3)	40 (25.0)
Morbidly obese (≥40)	48 (18.1)	8 (3.0)	34 (21.0)	5 (3.1)
Parity‡				
0	53 (19.9)	38 (14.2)	34 (21.1)	19 (11.7)
1	39 (14.7)	40 (15.0)	25 (15.5)	22 (13.6)
2	89 (33.5)	98 (36.7)	45 (28.0)	50 (30.9)
≥3	85 (32.0)	91 (34.1)	57 (35.4)	71 (43.8)
Cigarette smoking status§				
never	144 (59.0)	152 (56.9)	105 (66.9)	83 (51.6)
former	68 (27.9)	78 (29.2)	42 (26.8)	57 (35.4)
current	32 (13.1)	37 (13.9)	10 (6.4)	21 (13.0)
Diabetes	26 (9.7)	23 (8.6)	26 (16.1)	7 (4.3)
Hypertension	79 (29.5)	74 (27.6)	53 (33.7)	51 (31.5)

n = number

* missing for 4 cases and 1 control(all complex)

** missing for 19cases (15/4) and 23(14/9) controls

† missing for 2 cases (complex) and 3 controls (1 complex, 2 atypia)

‡ missing for 3 cases (2/1) and 1 control (complex)

§ missing for 29 cases (24/5) and 2 controls (1/1)

Table 2
Endometrial hyperplasia in relation to recent exogenous hormone use, by type of hyperplasia

	Cases n (%)	Endometrial Hyperplasia (Complex & Atypia Combined)	OR* (95% CI)	Complex Hyperplasia	Hyperplasia with Atypia
		Controls n (%)		n cases/ controls	n cases/ controls
			OR* (95% CI)	OR* (95% CI)	OR* (95% CI)
***-in the prior 6 months [§]					
OC use	266 (98.9)	253 (94.1)	1.0	169/161	97/92
No	3 (1.1)	16 (6.0)	0.2 (0.0–0.6)	3/11	0/5
Yes				1.0	1.0
-in the prior 6 months [‡]					
ET use	252 (83.2)	301 (99.3)	1.0	159/191	93/110
No	51 (16.8)	2 (0.7)	37.6 (8.8–160.0)	33/1	18/1
Yes				1.0	1.0
-in the prior 6 months [‡]					
EPT use	309 (88.3)	280 (80.0)	1.0	191/177	118/103
No	41 (11.7)	70 (20.0)	0.7 (0.4–1.1)	24/38	17/32
Yes				1.0	1.0
				0.8 (0.4–1.4)	0.6 (0.3–1.3)

n = number; OR = odds ratio; CI = confidence interval; OC = oral contraceptive; ET = estrogen-only hormone therapy; EPT = estrogen plus progestin hormone therapy

* adjusted for body mass index

** oral contraceptive use defined as OCs dispensed for > 1 month of use, all other hormone users excluded

[§] use in the six months prior to the date of onset of abnormal bleeding in the women with EH, or, for controls, the bleeding onset date for their matched cases

[‡] estrogen-only hormone therapy use defined as ET dispensed for ≥60 days of use, all other hormone users excluded

[‡] estrogen plus progestin hormone therapy use defined as estrogen dispensed for =60 days use and progestin dispensed for of =2 0 days of use, with total number of days of progestin at least one-third of the total number of days of estrogen, all other hormone users excluded