Menometrorrhagia in an Oral Contraceptive User

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Endometrial carcinoma is the most frequent malignancy of the female reproductive tract, and irregular vaginal bleeding is the most common presenting symptom. Endometrial carcinoma is found most commonly among postmenopausal women and is associated with obesity, nulliparity, and anovulation. Oral contraceptive (OC) use and tobacco smoking have been reported to protect against endometrial carcinoma.

Irregular vaginal bleeding is a common side effect of OC therapy. We report the case of an obese, premenopausal nulliparous woman with normal menses who developed menometrorrhagia and was then found to have endometrial carcinoma despite her youth and her use of both tobacco and combination OC.

Key words. Contraceptives, oral; endometrial neoplasms; tobacco; menstruation disorders; obesity, morbid.
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Irregular vaginal bleeding is one of the most common complaints with which oral contraceptive (OC) users present to their primary care provider. The use of combination OC has been reported to decrease a woman's risk of developing endometrial cancer. This protective effect is most notable among nulliparous OC users, whose relative risk is only 0.4 times that of nulliparous women who have never used OCs.[1] It is estimated that approximately 2000 cases of endometrial cancer are averted by past and current use of combination OC in the United States each year, especially in nulliparous women. The protective effect occurs in women who have used combination OCs for at least 12 months, and it persists for 10 years after cessation of the OC use. In addition, tobacco smoking decreases the risk of developing early-stage endometrial cancer.[2,3] The relative risk decreases by approximately 30% when one pack of cigarettes is smoked per day, and another 30% when more than one pack is smoked per day. The greatest reduction in risk is among the most obese smokers. Some have postulated an extra-ovarian mechanism for the anti-estrogen effect of smoking. Jensen and colleagues[4] found lower concentrations of serum estrogens in smokers than in nonsmokers, both of whom were treated with exogenous estrogens. The reported benefit of tobacco smoking in endometrial cancer is a caveat, however, considering the correlation between smoking and other malignancies, eg, carcinoma of the uterine cervix.

Case Report

A 30-year-old woman, gravida 0, para 0, presented with menometrorrhagia. The patient previously had had normal menses every 28 days since beginning menstruation at age 11 years. She had smoked one pack of cigarettes per day for 15 years, but denied alcohol intake. She had a history of significant central obesity since age 15. Her medical and family histories were otherwise unremarkable. At age 26 years she began a combination OC with 0.1 mg ethynodiol diacetate and 35 μg ethinyl estradiol for family planning. The patient noticed no menstrual irregularity for 4 years while taking OCs until she gradually developed menorrhagia. Her menorrhagia initially improved when her OC was changed to 0.3 mg norgestrel and 30 μg ethinyl estradiol for 6 months. She then developed early cycle metrorrhagia and was placed on 0.5 mg norgestrel and 50 μg ethinyl estradiol. She continued early and midcycle breakthrough vaginal bleeding with clots.

Physical examination, including pelvic and uterine examination, was unremarkable except for morbid obesity. The patient weighed 302 pounds. Results of a cervical Pap smear were normal. Hemoglobin was 13.7 g and a test for serum quantitative human chorionic gonadotropin was negative.

The vaginal bleeding continued and the patient was scheduled for hysteroscopy and fractional dilation and

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curettage the following week. Over the intervening weekend the bleeding increased and the patient presented to the emergency department. The uterus sounded to 14 cm. A large volume of curettings were consistent with grade 1 to 2, well-differentiated adenocarcinoma of the endometrium. Three weeks later the patient underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, and peritoneal biopsy for cytologic examination. The pelvis and abdomen were grossly free of metastatic disease. Pelvic and periaortic lymphadenectomies were not performed because of the lack of cervical involvement, the superficial nature of the disease, and the patient's body habitus. Histologic evaluation of the endometrium revealed a superficially invasive, well-differentiated adenocarcinoma consistent with stage IB, grade 1. Ploidy analysis revealed 12.5% tetraploid, with 0% aneuploid or hyperploid cells; 8.5% of the cells were in S phase and 21% in the proliferative phase. Both estrogen and progesterone receptors were positive. The patient's ploidy analysis and receptor status were consistent with the low-grade nature of the lesion. No postoperative radiation was recommended. The patient was doing well 6 months postoperatively.

Discussion

This case illustrates the quandary of the primary care provider dealing with irregular vaginal bleeding in a patient who is an OC user. After unsuccessful attempts at decreasing the estrogen effect and increasing the progestin effect, a diagnostic workup was begun. When hormonal manipulation has eliminated dysfunctional bleeding as the cause, one must pursue other less common causes, eg, infection, pregnancy-related, myoma, or malignancy. In most cases a biopsy can be accomplished in the office with an endometrial sampling device. Office testing was not successful in this patient, owing to her body habitus and discomfort.

When the possibility of cancer is being investigated by endometrial sampling, endocervical curettage is recommended to rule out cervical involvement. Only one third to one half of the patients with adenocarcinoma of the endometrium will have an abnormal Pap smear.

Endometrial cancer is the most common cancer in the female reproductive tract, affecting approximately 39,000 women each year, and is twice as common as carcinoma of the ovary or the cervix.[5] The most common presenting symptom is irregular vaginal bleeding. The median age is 61 years with the largest number of patients noted between the ages of 50 and 59 years. In 20% of postmenopausal women, uterovaginal bleeding is associated with a malignancy. If detected early, the 5-year survival rate for stage I endometrial cancer is 75%. Although endometrial cancer is very rare under the age of 30 years, the incidence in women under the age of 40 years has been reported to be from 2% to 14%.[6] A high index of suspicion must be maintained if the disease is to be diagnosed early in a young woman.

Endometrial hyperplasia and carcinoma have been associated with various sources of endogenous estrogen, eg, polycystic ovarian syndrome, granulosa cell tumors, ovarian thecomas, and adrenocortical hyperplasia, as well as unopposed exogenous estrogen replacement therapy.[5] The available evidence suggests that in predisposed individuals, the unopposed action of estrogen substances results in endometrial hyperplasia, anaplasia, carcinoma in situ, and, eventually, carcinoma.

This patient had some characteristics that are associated with increased risk for endometrial carcinoma and some with decreased risk. The common risk factors for endometrial carcinoma are nulliparity, obesity, anovulation, and late menopause, and frequently diabetes and hypertension. Two common factors that are protective against endometrial carcinoma are tobacco use and combination OC use. It was therefore unusual that this patient developed endometrial cancer, considering her age and history of combination OC use and smoking. Anovulation is a risk factor for endometrial cancer when associated with polycystic ovaries and increased estrogen levels, but not when anovulation is secondary to OC use. The patient's long history of obesity put her at increased risk for endometrial carcinoma.

The patient had a previously normal menstrual history and no signs or symptoms of polycystic ovarian syndrome. Lawrence and coworkers[2] found that the risk of endometrial cancer did not increase with body weight among smokers, whereas risk rapidly increased with body weight among nonsmokers. The Centers for Disease Control found the most notable protective effects of OC among nulliparas.[1]

Sequential OCs were removed from the commercial market in the 1970s because case reports and registry data revealed that endometrial cancer was disproportionately high among sequential OC users.[7] One sequential OC, Oracon, consisted of 0.1 mg ethinyl estradiol and 25 mg of the weak progestin dimethisterone, given in a sequential manner, rather than a combination pill. Several studies have indicated that the administration of unopposed estrogens to postmenopausal women is associated with an increased risk of endometrial hyperplasia and endometrial cancer.[8] Other studies have shown that the addition of sufficient progestin to the estrogen treatment regimen reverses this detrimental effect.[9]

This case illustrates that endometrial cancer can occur in a young woman taking combination OCs with a

significant history of morbid obesity. Obesity and nulliparity are the highest risk factors in younger women, though fortunately the tumor is usually of low stage and grade in these women.[6]

Irregular vaginal bleeding is not uncommon among OC users. A common management strategy for irregular vaginal bleeding is to alter estrogen or progestin effect, depending on what time in the cycle the bleeding occurs. Despite the reported protective effect of combination OCs, physicians should maintain a high index of suspicion about the cause of persistent irregular vaginal bleeding in all OC users, especially if obese. The workup is simple, well tolerated, and can be accomplished with a variety of office-based techniques.

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