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Original Article

Progesterone Challenge Test in Screening of Endometrial Pathologic Lesions in High-Risk Post-Menopausal Women

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Abstract

Objective: This study aimed to evaluate the prognostic value of the progesterone challenge test (PCT) in the diagnosis of hyperplastic and cancerous endometrium in high-risk postmenopausal women.

Materials and methods: In this cross-sectional study, 72 postmenopausal women without abnormal uterine bleeding who had risk factors for endometrial cancer were recruited. Patients with endometrial thickness of 4 mm or more as determined transvaginal ultrasonography were tested with progesterone challenge test. If there were any bleeding (spotting to severe bleeding) in the next two weeks, the test would be considered positive. After two weeks, all of the participants despite the result of PCT underwent office endometrial biopsy. In the end, all the results of PCT were compared with endometrial biopsy results.

Results: The mean age of the participants was 57.7 ±8.15 years. The progesterone challenge test was positive in 17 women (22%). Among the participants with positive progesterone challenge test, most of them show hyperplasia (62.5%) and 4.2% show endometrial cancer. According to the results, PCT had 37.5% accuracy, 20.8% sensitivity, 70.8 % specificity, 58.8% positive predictive value (PPV), and 30.9 % negative predictive value (NPV) for diagnosis of endometrial pathology.

Conclusion: We suggest that due to the unacceptable sensitivity and specificity of the PCT, this test alone is not suitable for screening of endometrial cancer or hyperplasia.

Keywords: Progesterone Challenge Test; Endometrial Hyperplasia; Endometrial Cancer

Introduction

Endometrial cancer is the most common gynecologic cancer in high-income countries and its incidence is increasing all over the world (1). The most important risk factor for endometrial cancer is unopposed estrogen exposure to the endometrium. The other risk factors such as obesity (2), diabetes (3), and the changes in fertility (for example increasing nulliparity) cause a rise in prevalence and number of deaths (1).

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In Iran, the reports show a rise in the prevalence of endometrial cancer (4, 5). According to comorbidity and risk factors, it seems necessary to use screening methods for early diagnosis and immediate decision for these women (6).

The most common symptom of endometrial cancer is usually abnormal uterine bleeding. Almost 90% of cancerous women, as the only symptom of disease, show bleeding or vaginal discharge (7). In the diagnosis process of endometrial cancer or hyperplasia, the most challenging group is asymptomatic women. Approximately 10% of women diagnosed with endometrial cancer do not present with post-menopausal bleeding (8).

One of the nonaggressive methods which can be used for screening of endometrial pathologic lesions is transvaginal ultrasonography. Unfortunately in asymptomatic menopausal women transvaginal ultrasonography has not high accuracy in diagnosis (9).

Yet there is no accurate, cost-benefit, and non-aggressive screening method for asymptomatic menopausal women. Routine biopsy is not acceptable as a screening method because it is aggressive and expensive. Routine ultrasonography is not a suitable test either in terms of diagnostic value or economic burden. On the other hand, early diagnosis of hyperplasia or even endometrial cancer in the early stage of disease when the disease is still limited to uterus can increase the patient's survival. So, using accurate and appropriate diagnostic tests can cause exact diagnosis, timely treatment, and a high rate of recovery (10).

The progesterone challenge test (PCT) is a test that has been used for the evaluation of amenorrhea patients. This test shows whether the endometrium has had exposure to estrogen or not? (11) If the serum estradiol level is adequate (over 50 pg/ml), and the endometrium is in the proliferative phase, withdrawal bleeding will happen in 2 -7 days after progesterone withdrawal. As we mentioned above, one of the important risk factors of endometrial cancer and hyperplasia is a higher serum estrogen level. So, this hypothesis is proposed that maybe PCT can be used as a simple, nonaggressive, cheap test (12). The accuracy of PCT in endometrial cancer or hyperplasia diagnosis has been evaluated in several studies and the sensitivity of this test in asymptomatic menopausal women varies from 37 to 100% (13, 14). In the case of specificity, the results were inconsistent.

We decided to evaluate if PCT is proper for diagnosis of endometrial hyperplasia or cancer? And can we use PCT as a screening method in menopausal women especially high-risk ones?

Materials and methods

This cross-sectional study was conducted in Arash Hospital, Tehran, Iran from January 2019 to June 2021. The study was approved by the ethics committee of Tehran University of Medical Sciences, Tehran, Iran with the code number (IR.TUMS.MEDICINE.REC.1399.1219). All participants signed informed consent. The study was performed on 72 postmenopausal women without a history of bleeding who visited Arash Hospital's clinic. Women older than 40 years with normal pelvic examination and no history of hormonal therapy, with at least one year of amenorrhea from the last menstrual bleeding, a Follicle-stimulating hormone (FSH) level of over 40, without a history of bleeding or contraindication for consuming progesterone were eligible to enter the study. In this study high-risk criteria for endometrial cancer included at least one of the following factors: high BMI, past history of PCOS, HTN, Diabetes Mellitus, hypothyroidism, consuming nonopposed estrogen, familial history of endometrial cancer, consuming Tamoxifen, Lynch`s syndrome, irregular menstrual bleeding, oligomenorrhea, late menopause, early menarche. The exclusion criteria were patients with a past history of thromboembolism and severe hepatic disease.

All of patients were examined with transvaginal ultrasonography to evaluate endometrial thickness. Transvaginal ultrasonography was performed with Philips affinity 70 machine by the same examiner. If the thickness was 4 mm and more, 100 mg progesterone ampule (Fertigest 50, Iran Hormone, Iran) was administered.

The test was considered positive if any sign of bleeding (spotting or bleeding) occurred over the next 2 weeks. After the 2 weeks, all patients regardless of PCT test underwent office endometrial biopsy.

At last, the results of ultrasonography, pathology, and PCT test were evaluated. For result reporting we used average and Standard deviation for qualitative variables and numbers (percentage) for quantitative variables, for examining the accuracy of PCT test PPV and NPV. All the statistics were analyzed with SPSS software (version 16) and the statically significant level P-value was considered less than 0.05. For the specificity and sensitivity of PCT (as a two-state variable) we used pathology reports as the gold standard.

Results

During the studied period, 72 women were eligible based on inclusion criteria. Table 1 shows the participant's basic characteristics. The average age of patients was 57.7± 8.15 years, the menarche age was 10.24±1.48 years, and the menopause age was 49.66± 4.73 years either. The average of their BMI was 30.72±5.57 kg/$m2$, the average number of pregnancies was 3.92±1.86 and the average number of deliveries was 3.57±1.74. The most documented risk factor was hypertension with a prevalence of 47.7%.

Table 1: Patient's basic characteristics

Variables	Participants
Age(years): Mean ±SD	57.7±8.15
Menarche Age: Mean ±SD	10.24±1.48
Menopause Age: Mean ±SD	49.66±4.73
BMI: Mean ±SD	30.72±5.57
Number of pregnancies: Mean ±SD	3.92±1.86
Number of deliveries: Mean ±SD	6.57±1.74
Marital status: No (%)	
Married	77(98.7%)
Single	1(1.3%)
Type of delivery: No (%)	
Nulliparous	3(3.8%)
Cesarean	9(11.5%)
Normal vaginal delivery	48(61.5%)
Both	18(23.1%)
Contraception: No (%)	
Withdrawal	3(3.8%)
IUD	9(11.5%)
OC	48(61.5%)
Vasectomy/TL	15(23.1%)
DMPA	3(3.8%)
Risk factors of endometrial cancer: No (%)	
Diabetes Mellitus	25(32.1%)
Hypertension	39(47.7%)
PCOD	9(11.5%)
Hypothyroidism	28(35.9%)
Past history of breast cancer	9(11.5%)
Familial history of breast cancer	18(23.1%)
Tamoxifen usage	10(12.8%)

†Based on t-test; *Based on Chi-Square test; IUD: Intrauterine device; OC: Oral contraceptives; TL: Tubal ligation; DMPA: Depot medroxyprogesterone acetate; PCOD: Polycystic ovarian disease

At the end of this study, 17 patients (22%) experienced vaginal bleeding after using progesterone. The severity of bleeding in most patients was spotting (64.7%). The duration of bleeding in 41.1% of patients was 2-5 days and at least 60% had bleeding over 6 days. Pathology results revealed that most of the participants showed endometrial hyperplasia (62.5%) and the prevalence of endometrial cancer was 4.2%.

To evaluate the validity of the progesterone challenge test, the result of this study was compared with the histopathological findings of endometrial biopsy. The accuracy, sensitivity, specificity, PPV, and NPV of this test were 37.5%, 20.8%, 70.8%, 58.8%, and 30.9% respectively. After the separation of cancer and endometrial hyperplasia, the accuracy, sensitivity, specificity, PPV, and NPV of the test were 36.2%, 17.7%, 70.8%, 53%, and 31.4% respectively. The accuracy, sensitivity, specificity, PPV and NPV for endometrial cancer were 77.7%, 66.7%, 78.2%, 11.7%, and 98.2% respectively (Table 2).

Table 2: Accuracy in diagnosing different types of endometrial lesions

	Endometrial cancer	Endometrial hyperplasia	Endometrial pathologies
Accuracy	77.7%	36.2%	37.5%
Sensitivity	67.7%	17.7%	20.8%
Specificity	78.2%	70.8%	70.8%
PPV	11.7%	53%	58.8%
NPV	98.2%	31.4%	30.9%

Discussion

The results showed that the diagnostic value of PCT for the diagnosis of endometrial pathologies was very low and unacceptable. After the separation of endometrial cancer from endometrial hyperplasia and separate recalculation of the parameters of diagnostic value, according to lower numbers of endometrial cancer, results showed no obvious difference. However, the diagnostic value of parameters for the diagnosis of endometrial cancer from benign or normal cases was acceptable. The PCT with an NPV of 98.2% can predict nearly 100% of cases of endometrial cancer. However, in endometrial hyperplasia, the function of the test with NPV 31.4% even in the diagnosis of normal cases was also not acceptable.

PCT is used as a screening test in asymptomatic menopausal women especially in women who are high risk for endometrial hyperplasia.

For the first time using the PCT for evaluation of endometrial proliferation, bleeding after stopping the use of progesterone, was suggested in1980 by Gambrell&co., for the evaluation of the risk of endometrial cancer in asymptomatic menopausal

women (15). However, in that paper correlation between laboratory results and endometrial pathology was not a concern. In the next articles the same author, was emphasized on the usefulness of tests and the evaluation of test efficiency in the USA became popular (16).

According to the result of these studies, the sensitivity of PCT in asymptomatic menopause women was variable (37-100%) and specificity was the same. Although, the results of most studies showed that the specificity of the test was very high (nearly 100%), but in three studies of Toppasada, Chu, and KWACK showed specificity respectively 92%, 78%, 78%, and the specificity of the test was lower. (17) (18, 19)

Several researchers recommended using PCT and transvaginal ultrasonography (TVUS) for the diagnosis of endometrial cancer in the postmenopausal period. Even some of these researchers such as Ivanov, who analyzed several tests, found better results with PCT and TVUS (20) , Some researchers such as Lo`pez preferred PCT to TVUS in asymptomatic post-menopause women who used Tamoxifen (21).

As previously mentioned, the function of PCT is as follows, if the endometrium had been opposed to estrogen or if the endometrium was in proliferation phase PCT will cause shedding and bleeding. According to this if the endometrium was atrophic due to the menopause period, the shedding would not occur, so the number of false negatives was very low, and the specificity of the test was over 90%. The Chu and Kwak finding was similar to our study and they reported very low specificity and sensitivity for test (18, 19)

Another important difference between our and previous studies is the kind of sample we examined, most of the previous studies, were performed without noticing previous exposure of participants to risk factors, and only in El-Maraghy study (12) women with underlying diseases such as diabetes and hypertension, and in Lo`pez study (21), a patient who used Tamoxifen were considered. According to this reason, the number of diagnosed cancers in our study was higher, asymptomatic while, in none of the other studies, endometrial cancer was not diagnosed in histopathology and only one case of endometrial cancer was reported in El-Maraghy study (12).

The last issue is the average time used for considering PCT positive, in almost all of the previous studies except Lo`pez study ;(21) who consider PCT test positive if bleeding occurs in one month after using progesterone; others considered PCT positive if bleeding occurs in 2 weeks. In our study at first the time that we considered, was 2 weeks for occurring bleeding; but in 2 patients who were diagnosed with endometrial cancer, bleeding occurred after 2 weeks of PCT, so may be considering the longer period for evaluation of bleeding or an even higher dose of progesterone can reduce false negative cases. One of the limitations of our study was the small sample size, and it seems that conducting more studies with a larger sample size would be helpful for a more accurate assessment.

Conclusion

According to the result of this study, contrary to all the previous studies, the diagnostic value of the PCT for the diagnosis of endometrial pathologies was very low and unacceptable; although after separating endometrial cancer and hyperplasia and recalculating separately, the diagnostic value and differentiation power of endometrial cancer from normal or benign lesions was more acceptable and showed higher NPV. The PCT with NPV 98.2% can predict near to 100% of patients without cancer. A higher NPV of PCT at the end of the study, helps us to roll out the malignant changes and in the future periodic usage of this method can help us confidentially evaluate endometrium for serious pathology without any aggressive technique. As a result, it is suggested, that similar studies use higher sample sizes, and in future studies use more trustworthy methods such as hysteroscopy and targeted endometrial biopsy for evaluation.

Conflict of Interests

Authors declare no conflict of interests.

Acknowledgments

This study was approved by the ethics committee of the Tehran University of Medical Sciences, Tehran, Iran. All participants signed an informed consent.

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