Evaluation of Endometrial Thickness in asymptomatic Postmenopausal Women with Hypertension

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ABSTRACT

Background: Endometrial cancer is a common gynecological malignancy and endometrial hyperplasia is its precursor.

Objective: To examine whether the endometrium of hypertensive asymptomatic postmenopausal women is thicker than that of non-hypertensive asymptomatic postmenopausal women, to determine whether this thickening is directly related to the antihypertensive drugs and whether it's associated with abnormal pathology.

Methods: A case-control study of seventy asymptomatic postmenopausal women was conducted in Al Yarmouk Teaching Hospital, Department of Obstetrics and Gynecology, during the period from 1st September 2017 to end of June 2018. Forty-five women were hypertensive and twenty five were non-hypertensive. Twenty-two women of hypertensive group were treated with β-blockers combination medication and twenty-three women were treated with other antihypertensive medications. They were compared with each other and with those twenty five women of non-hypertensive group. All women were interviewed and examined; blood tests were performed and endometrial thickness in antero-posterior diameter was measured by vaginal ultrasonography. Endometrial sampling had been taken only for those with increased endometrial thickness more than 4 mm.

Results: About twenty four percentage (24.44%) of hypertensive women and four percentage (4%) of non-hypertensive women had an endometrial thickness >4mm which was significant difference, whereas there was no statistically significant difference in endometrial thickness between those who treated with medication including β-blocker and those who were treated with other medication. The histological findings were mainly of endometrial hyperplasia for those with endometrial thickness >4mm.

Conclusion: Hypertension in asymptomatic post-menopausal women increased the endometrial thickness. However, we were unable to substantiate an association between the type of treatment administered and the increased in the endometrial thickness. Those with increased endometrial thickness more than 4 mm, the histological findings were mainly of endometrial hyperplasia.

Keywords: **Hypertension, Menopausal women, Endometrial hyperplasia.**

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Endometrial cancer is the fourth most common cancer ranking behind breast, lung and bowel cancer and it's the eighth leading cause of death from malignancy in women. It's now the commonest gynecological malignancy. The disease affects mainly postmenopausal women however approximately 20% of cases occur in premenopausal women[1-3].

A possible mechanism that might be responsible for endometrial thickness in patient with hypertension, as well as in those with obesity and glucose intolerance is that of hyperinsulinemia, insulin resistance and hence to insulin like growth factor 1, which has been related to cell growth and neoplastic progression[4,5]. Long-term treatment with conventional β-blockers either non-selective, or β_1-selective, significantly decreased insulin sensitivity in hypertensive women. They alter the insulin secretion from pancreatic β-cells which plays an important role in controlling post load glycaemia, so that

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more insulin is needed. β-blockers also attenuate insulin in insulin resistant patients leading to >10% higher steady state plasma insulin level; the resulting hyperinsulinemia could down regulate the insulin receptors and consequently lower insulin sensitivity[4,6,7]. Transvaginal ultrasound is more accurate in delineating endometrial thickness. No endometrial thickness threshold completely excludes the possibility of an early endometrial carcinoma, which can be present in women who have no postmenopausal bleeding (PMB), but have been scanned for other reasons and found to have a thickened endometrium as an incidental finding [8-10]. Endometrial aspiration has the advantage that it can be done as an outpatient procedure. Many physicians generally perform the endometrial biopsy without anesthesia, and most patients are able to tolerate this well. However, the use of a para cervical block, as well as non-steroidal anti-inflammatory drugs, greatly improves the patient tolerance and compliance[11].

The aims of the study is to find whether the endometrium of hypertensive postmenopausal women is thicker than that of non-hypertensive women by using transvaginal ultrasound for measuring the thickness of the endometrium. To assess the effect of antihypertensive drugs on endometrial thickening. To find if there is significant endometrial abnormalities when endometrial thickness more than 4 mm by endometrial sampling.

——————————Methods

A case-control study was conducted at Al-Yarmouk Teaching Hospital in the time period between 1st September 2017 to 30th June 2018. Seventy asymptomatic women with no history of postmenopausal bleeding (PMB), who were at least one year after menopause were considered for enrollment in this study and divided in to the following three groups:

I. Women without hypertension.

II. Women with essential hypertension treated with a combination of medication including β-blockers.

III. Women with essential hypertension treated with other medication that did not include β-blockers.

The non-hypertensive control women were those who came for a routine gynecologic examination or who complained of gynecological symptoms other than vaginal bleeding, like vaginal discharge of genital infection, symptoms of urinary tract infection or symptoms of pelvic organ prolapsed. Women with essential hypertension treated with medication for at least one- year duration were enrolled from the medical clinic. Specially designed questionnaire was used. Women were interviewed for a history of infertility, hormonal disturbance, smoking, and medical diseases. Blood pressure, weight and height were measured then body mass index (BMI) was calculated. Blood tests for fasting blood sugar and follicular stimulating hormone (FSH) level were performed. Vaginal ultrasonography with a 7.5 MHz probe was then performed for measuring the endometrial thickness in anteror-posterior diameter and to exclude an ovarian pathology. For the purpose of this study, an endometrial thickness more than 4 mm was considered thick. Endometrial sample was taken from a woman with a thickened endometrium and sent for histopathology. The sample was taken by endometrial aspiration (pipelle) as an outpatient endometrial biopsy and if the patient refused or the procedure failed to obtain a biopsy because of cervical stenosis, then dilatation and curettage was done under general anesthesia.

Exclusion criteria:

- Diabetic women or women with an abnormal fasting blood sugar level.
- Obese women (BMI >30).
- Women who had been taken hormonal medications or hormonal replacement therapy during the last year.
- Women with a history of hormonal disturbance, infertility or polycystic ovarian syndrome.

- Women with any malignant disease or ovarian tumor, whether benign or malignant.
- Smokers or who had smoked during the past year.

The number of each group of the participants was:

I. Women without hypertension (number =25).

II. Women with essential hypertension treated with a combination of medication including β-blockers (number=22).

III. Women with essential hypertension treated with other medication number= (23).

The significance of differences of different percentage (data) was tested using person Chi- squared test (x^2- test). The significance of differences for two independent means was tested using t-test. Statistical analysis was considered significant when the P-value was less than 0.05.

Results

A total of seventy women were considered for enrollment in this study. The age of the participants is ranged between 50 and 68 years. Forty-five women with hypertension enrolled in the study: 22 were treated with a combination of medication including β-blockers and 23 were treated with other medications. The two groups were compared with a group of 25 non-hypertensive women.

As shown in Table 1, both hypertensive groups were similar to the control group in all aspects.

Table 2, shows that although a diastolic blood pressure was similar among all women as a result of treatment for hypertension, the systolic blood pressure was higher among the hypertensive group. There was no significant difference in BMI between the hypertensive group and non-hypertensive group.

As shown in table 3, there was significant difference in FBS level between each group of hypertensive women and that of non-hypertensive group. It was higher in the hypertensive group, but there was no significant difference in FBS level between each group of hypertensive women. FSH level was similar among the three groups.

Table 3, also, showed that there was significant difference in endometrial thickness between each group of hypertensive women and that of the non-hypertensive group, but there was no significant difference in endometrial thickness between women treated with β-blockers medication and those who treated with other medication.

As shown in figure 1, the percentage of women with endometrial thickness (>4mm) in hypertensive group was 24.44%, while that of non-hypertensive group was 4% which means that there was a significant difference between the two groups by using Pearson Chi-squared test.

Table 1: Characteristics of patient's medical history.

	Non-hypertensive group N=25	Hypertensive group (N=45)		
		With β-blocker combination medication	With other combination medication	Total
Age (years) ±SD	61.60±4.97 (55-68)	62.68±5.22 (53-67)	62.87±5.36 (50-67)	62.78±5.23 (50-67)
Age at menopause (years) ±SD	51.96±1.40 (48-54)	51.50±1.37 (49-54)	51.57±1.31 (48-54)	51.53±1.32 (48-54)
Age at menarche (years) ±SD	12.80±0.76 (12-14)	12.91±0.97 (11-14)	12.57±0.95 (11-14)	12.73±0.96 (11-14)
Parity (number)±SD	8.68±1.68 (4.0-12.0)	8.09±1.54 (4.0-12.0)	8.22±1.68 (4.0-12.0)	8.16±1.59 (4.0-12.0)

Data presented as mean ±SD (range). *Significant difference from non-hypertensive using t-test for two independent means at 0.05 level of significance. # Significant difference from hypertensive with β-blocker combination medication using t-test for two independent means at 0.05 level of significance. Each of the three groups was compared with one another by using student-t-test.

Table 2: Patient's physical characteristic.

	Non-hypertensive group N=25	Hypertensive group N=45		
		With B-blocker combination medication	With other combination medication	Total
BMI±SD	27.33±0.34 (26.6-28.1)	27.51±0.83 (25.8-29.1)	27.04±1.18 (25.4-29.0)	27.45±1.05 (25.4-29.1)
SBP (mmHg)±SD	129.80±3.38 (120.0-135.0)	149.55±7.85* (140.0-160.0)	150.43±8.25* (140.0-160.0)	150.00±7.98* (140.0-160.0)
DBP (mmHg) ±SD	79.80±2.27 (70.0-85.0)	80.45±6.35 (70.0-90.0)	81.83±5.80 (70.0-90.0)	81.67±6.12 (70.0-90.0)

Data presented as mean ±SD (range).
*Significant difference from non-hypertensive using t-test for two independent means at 0.05 level of significance.

Table 3: Laboratory and ultrasonography findings.

	Non-hypertensive group N=25	Hypertensive group N=45		
		With B-blocker combination medication	With other combination medication	Total
FBS level (mg/dl)±SD	90.80±3.44 (80.0-100.0)	100.45±5.10* (90.0-110.0)	99.35±5.07* (90.0-110.0)	*99.89±5.06 (90.0-110.0)
FSH level (mIU/ml) ±SD	61.04±11.36 (40.0-70.0)	59.68±10.96 (40.0-70.0)	60.78±9.14 (40.0-70.0)	60.24±9.97 (40.0-70.0)
Endometrial thickness (mm) ±SD	2.32±0.85 (2.0-6.0)	6.55±5.52* (3.0-22.0)	6.39±6.46* (2.0-25.0)	6.47±5.95* (2.0-25.0)

Data presented as mean ±SD (range).
*Significant difference from non-hypertensive using t-test for two independent means at 0.05 level of significance.
#Significant difference from hypertensive with β-blocker combination medication using t-test for two independent means at 0.05 level of significance.

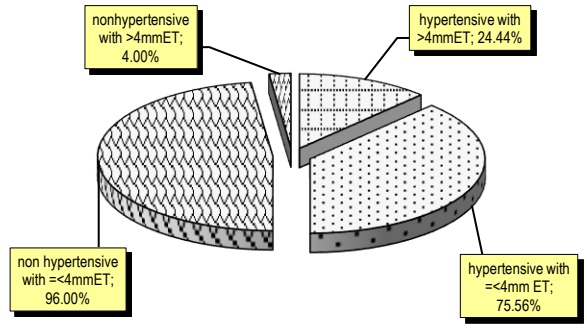

Figure 1: The percentage of endometrial thickness in the two groups (using Pearson chi- squared test, P = 0.030).

The histological findings of endometrial biopsies: In hypertensive group, the total number was 45 patients, eleven of them had endometrial thickness more than 5 mm and the histological findings were: Seven samples were (endometrial hyperplasia without atypia). One sample (endometrial hyperplasia with atypia). Two samples (non-secretary endometrium), and the last one (proliferative endometrium).

In non-hypertensive women (total number 25) only one patient had endometrial thickness >5 mm and the histological finding was non-secretary endometrium.

——————————Discussion

Screening for endometrial cancer or its precursors may be justified for certain high-risk women such as those receiving postmenopausal estrogen therapies without progestin. The apparent association between hypertension and endometrial cancer had been repeatedly arisen over the years. Tranvaginal ultrasound is a noninvasive method that yield detailed image of the uterus[12]. The main finding in this study was that 24.44% of the asymptomatic post- menopausal women, who were hypertensive, had increased endometrial thickness whereas only 4% of non-hypertensive women had increased endometrial thickness which was significant. The cutoff point of endometrial thickness in this study was 4 mm. Other risk factors that may influence hypertension or may affect the endometrial thickness like (diabetes, obesity, hormonal effects, and smoking) had been excluded in this study.

This was in agreement with a study done by Jacob Bornstein who concluded that 20% of hypertensive postmenopausal women were found to have increased endometrial thickness, forty five hypertensive women were enrolled in the study and other risk factors for endometrial cancer had been excluded[5]. Our study was unable to verify a significant association between the type of treatment administered whether β-blockers were included or not and the increase in endometrial thickness which was in agreement with a study done by Jacob Bornstein[5]. A network of case-control studies by Maria Soler et al about the relation between hypertension and the risk of selected hormone related neoplasm in women, showed a significant association of postmenopausal breast cancer and endometrial cancer with hypertension, while no significant association was observed for ovarian and thyroid cancer. Confounding effect of several covariates, including age, area of residence, education, tobacco smoking, alcohol consumption, parity, and BMI (more than 30 kg/m^2), was controlled for, in the analysis. The possible interpretation for breast cancer includes the relation between treatment for hypertension and increased secretion of prolactin, a hormone with recognized effect on breast tissue differentiation[15].

A possible mechanism that may be responsible for endometrial thickness in hypertensive women is that of hyperinsulinemia and insulin resistance[4]. The treatment with conventional β-blockers had detrimental effect on insulin sensitivity; this can be seen from several studies[4]. In large prospective atherosclerosis risk in communities cohort study after adjustment for all potentially important confounders showed that those treated with β-blockers had 28% higher risk of type 2 diabetes, compared to those taking no medication, whereas users of thiazide diuretics, angiotensin converting enzyme inhibitors or calcium channel blockers were not at significantly higher or lower risk for subsequent type 2 diabetes than untreated hypertensive[13]. Originally, it was intended to enroll an additional group of untreated hypertensive women to distinguish between the role of hypertension itself and that of medication. Unfortunately, it becomes clear that in most cases the treatment was initiated on discovery of hypertension and that's the reason we couldn't enroll a sufficient number of untreated hypertensive women. In this study, the endometrium of a woman with more than 4 mm thickness was sampled to find whether it was associated with significant endometrial abnormality. Endometrial hyperplasia are generally considered premalignant disorders of the uterus which are clinically important because they may cause abnormal bleeding and precede or occur simultaneously with endometrial cancer[14]. Clinically significant hyperplasia usually evolves within a background of proliferative endometrium as a result of protracted estrogen stimulation in the absence of progestin influence[1,14]. Our study showed that there was significant difference in

fasting blood sugar (FBS) level between hypertensive and non-hypertensive groups which was higher in the former group, this may be explained by the concept of metabolic syndrome which suggests that a decrease in insulin sensitivity would not result in elevation of blood glucose level as long as pancreatic β-cells would secrete the necessary amount of insulin, however after a certain period of time, β-cells would no longer be able to compensate for the increase in insulin resistance and type 2 diabetes would appear. The decrease in insulin sensitivity may be caused by the anti-hypertensive drugs or the hypertension itself[4].

In conclusion; Hypertensive asymptomatic postmenopausal women were found to have increased endometrial thickness, which is assessed by TVUS when other risk factors (diabetes, obesity, hormonal effect) have been excluded. We were unable to substantiate an association between the type of the treatment whether β-blockers included or not and the increase in the endometrial thickness.

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