The role of hypertension, body mass index, and serum leptin levels in patients with endometrial hyperplasia during premenopausal period

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Summary

Objectives: to investigate whether body mass index (BMI), hypertension (HTN), diabetes, age, and physical activity can be considered risk factors for endometrial simple hyperplasia in premenopausal women. Furthermore this study was undertaken to determine whether serum concentration of leptin in patients with BMI ≥ 30 kg / m² with endometrial hyperplasia deviate from values in patients with normal endometrium. *Materials and Methods:* The authors enrolled 167 hyperplasia cases and 282 controls. Demographic characteristics and data on age, diabetes, hypertension, BMI, physical activity, and anthropometric parameters were collected. Leptin concentration in serum was measured with immunoenzymatic test kit from IBL. Univariable and multivariable analysis were performed to verify the association among age, HTN, BMI, physical activity, diabetes, and the presence of uterine hyperplasia. Furthermore the authors evaluated the correlation between BMI and leptin level (with Pearson's linear correlation) in women with simple hyperplasia and in controls. *Results:* The prevalence of hyperplasia found was 34.4%. The following factors were independently associated with increased risk of endometrial hyperplasia: HTN (odds ratio 3.19, 95% confidence interval 1.20 - 8.48, $p < 0.020$) and BMI ≥ 30 Kg / m² (odds ratio 6.43, 95% confidence interval 3.92 - 10.53, $p < 0.000$). Mean leptin concentration in serum was higher in patients who had endometrial hyperplasia than in controls ($p < 0.005$) and the leptin levels depended on BMI. *Conclusions:* The following are risk factors for endometrial hyperplasia in premenopausal women: BMI ≥ 30 kg / m² and HTN (blood pressure ≥ 130 / 85 or in therapy). Leptin appears to participate in proliferative processes of the endometrium, depending on BMI. Current guidelines may need to be reconsidered.

Key words: Diabetes; BMI; Hypertension; Endometrial hyperplasia; Leptin.

Introduction

Endometrial diseases in premenopausal women with abnormal bleeding is not common. The incidence of endometrial hyperplasia in premenopausal women is reported to be 2% to 10% [1, 2], but endometrial hyperplasia incidence with and without atypia peaks during early postmenopausal years and in early 1960s women, often in association with abnormal uterine bleeding (AUB) [3].

Endometrial hyperplasia has been classified into three main types: 1) simple hyperplasia, characterized by minimal endometrial glandular crowding and with low risk of progression to endometrial carcinoma; 2) complex hyperplasia, characterized by greater endometrial glandular crowding and intermediate risk of progression; and 3) atypical hyperplasia, characterized by an endometrium with complex glandular crowding and / or cytologic atypia, and the greatest risk of endometrial carcinoma progression [4, 5].

The diagnoses of endometrial hyperplasia are only made in women who have had endometrial sampling. Due to the invasive nature of endometrial sampling, very few studies have performed routine endometrial biopsies on asymptomatic women [6, 7]. These researches show that among women with normal bleeding patterns, the prevalence of simple and complex hyperplasia is 0.5% to 5% and the prevalence of atypical endometrial hyperplasia or carcinoma is less than 1%.

Rapid lifestyle changes in modern society have produced an epidemic of obesity implicated in diabetes and hypertension. All three conditions are included among risk factors of endometrial cancer as established by many studies [8, 9].

Although the risk factors for endometrial hyperplasia in postmenopausal women have been well-established [10], they do not apply to premenopausal women. A retrospective study report of 46 premenopausal women found that body weight, age, infertility, family history of colonic carcinoma, and nulliparity were risk factors for endometrial hyperplasia [11].

The purpose of this study was to analyze possible associations between simple endometrial hyperplasia in perimenopausal women and adipose tissue distribution: evaluating BMI, hip and waist circumferences, waist to hip ratio (WHR), leptin concentration, hypertension (HTN), diabetes, and life style.

Materials and Methods

All premenopausal women, who had menstrual irregularity for one or two years associated with hot flashes or night sweats, ranged from 40 to 55 years (mean 48.2 years) going to the

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gynaecologic assessment unit at St. Anna and St. Sebastiano's Hospitals of Caserta between June 2009 and June 2011, were identified and were invited to participate in this study. The informed consent was obtained from the partecipants before entry. A total of 639 patients were referred to the Department with abnormal bleeding or endometrial abnormalities disclosed at sonografy (dishomogeneous echo pattern, absence of central echo or presence of focal lesions). One hundred fifty-six patients (24.4%) had abnormal bleeding and 483 (75.6%) patients were asymptomatic.

Exclusion criteria were as follows: (1) amenorrhea ≥ one year; (2) gynaecological organic pathologies, such as diagnosis of endometrial cancer or history of endometritis or annexial flogosis; (3) patients receiving hormonal therapy or exposed previously to exogenous estrogens. Patients with an intrauterine device (IUD), or who had received hormonal treatment in the previous three months, or who had already undergone dilatation and curettage (D&C) or diagnostic or operative hysteroscopy were excluded from the analysis. Inclusion criteria were as follows: (1) premenopausal women between 40 and 55 years-old who complained of abnormal uterine bleeding > three months (heavy menstrual bleeding, irregular or intermestrual bleeding) regardless of cycle; (3) abnormal ultrasonographic pattern (endometrial hyperechogenic spots, irregular endometrial line, suggestion of uterine septa).

The authors invited participants to describe AUB symptoms using a specified simple list of four terms with three choices of descriptive words for each term. The four keys were: cycle regularity (specified as irregular, regular or absent), frequency of menstruation (specified as frequent, normal or infrequent), duration (specified as prolonged, normal or shortened) and volume of menstrual flow (specified as heavy, normal or light) [12].

Past obstetric and medical history, as well as ongoing pharmacological therapy, were recorded. The authors used ultrasonography as first step in all patients (n = 639) to evaluate possible abnormal patterns. Ultrasonography was performed by gynaecologists independently of the phase of the cycle. The ultrasound finding was considered abnormal when the technician visualized a lesion inside the cavity or when the maximum endometrial thickness measured in the sagittal plane according to the technique of Ozdemir *et al*. was > 8 mm [13]. Doubtful sonograms with findings neither definitively negative nor positive, due to poor visualization and / or difficult interpretation were considered abnormal. The gynaecologist found 97 (15.2%) submucous myoma (diagnosed at ultrasonography in the presence of a nodular formation with well-defined margins, heterogeneous structure, and varying echogenicity, which displaced the endometrial lining) and 57 (8.9%) endometrial polyps . The authors treated these patients by running the diagnostic hysteroscopy and later surgery as needed, but have not included them in the study. The authors found 282 (44.1%) patients with normal sonography pattern and 203 (31.8%) with abnormal pattern.

All women were submitted to hysteroscopy to assess abnormal uterine bleeding or abnormal sonographic patterns. The inclusion of both symptomatic and asymptomatic patients, provided a better estimation of endometrial hyperplasia prevalence within the general population. Hysteroscopy was always carried out in sterile conditions after cleansing of external genitalia, vagina, and cervix with a povidone iodine antiseptic solution. The investigation was postponed if an acute cervico-vaginal infection was present. Diagnostic hysteroscopy was performed by a gynaecologist, with a 5 mm Storz hysteroscope (Karl Storz, Tuttingen, Germany). The vaginoscopic approach

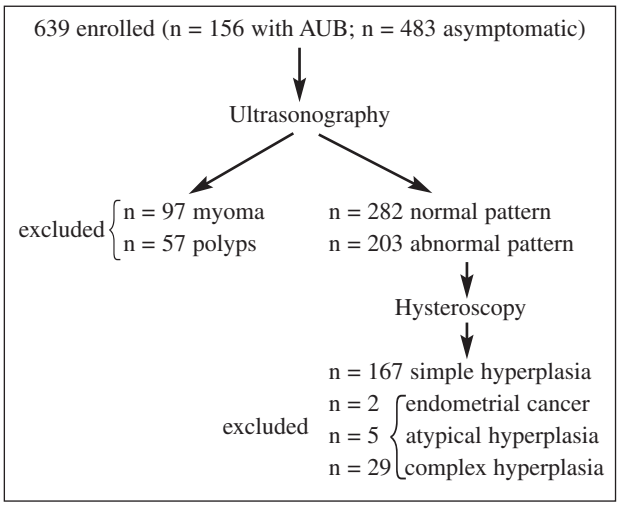

Figure 1. — Patient allocation according to histological results.

(without speculum) was used to avoid patient discomfort or pain not directly related to uterine examination. The investigation was postponed if an acute cervico-vaginal infection was present. Only in women with a history of previous pelvic inflammatory disease was a single prophylactic two gram dose of cefoxitin injected i.m. 30 minutes before hysteroscopy. Endometrial hyperplasia was defined, macroscopically, as thick, hyper-vascular, friable mucosa that was mamillated or polypoid. At the end of the procedure, an intrauterine biopsy was obtained with a small cutting curette [14]. The diagnosis of uterine hyperplasia was histologically made by the pathologist of the Department of Pathology of St. Anna and St. Sebastiano Hospitals.

Histologic diagnosis of the endometrium distinguished between normal findings (n = 282), with abnormal findings (n = 203): 167 (34.4%) cases were simple hyperplasia, two (0.4%) endometrial carcinoma, five (1%) hyperplasia with atypia, and 29 (6%) were complex hyperplasia. The samples of carcinoma, complex hyperplasia, and atypic hyperplasia were not included in this study. Depending on the results of histology, patients were allocated into one of two groups: group I (n = 167) simple hyperplasia and group II (n = 282) control patients with normal endometrium (endometrium in secretory stage, endometrium in proliferative stage) (Figure 1).

A general physical including a gynecological examination were performed. Anthropometric measurements and other data were recorded. The authors evaluated: body weight, height, BMI, leptin levels, waist and hip circumferences, WHR, fasting glucose, blood pressure, and the quality of physical activity.

Body weight was measured, in underwear, to the nearest kilogram with a balance scale. Height was measured to the nearest centimeter. The authors used a Seca 200 scale (Seca, Hamburg, Germany) with attacked stadiometer. BMI was calculated as weight / height^2 (kg / m^2). Leptin concentrations in serum were measured with immunoenzymatic test kit from immuno-biological laboratories (IBL). Waist circumference was measured, using a steel tape measure, to the nearest centimeter at a level midway between the lower rib margin and iliac crest. Hip circumference was measured at the widest point between hips and buttocks. Measurements were taken in the upright position. WHR was calculated as waist circumference in centimeters divided by hip circumference in centimeters. WHR > 0.8 was considered abnormal in women [15]. Fasting glucose was measured in all patients (n = 485) and assays for glucose was performed in the hospital's chemistry laboratory.

Table 1. — *Leptin concentration in serum depending on BMI in groups I and II.*

	BMI < 30	BMI ≥ 30
Group I	7.8 ng / ml	13.5 ng / ml
Group II	3.2 ng / ml	7.8 ng / ml
p (I vs II)	< 0.005	< 0.005

Table 2. — *Independent sample test: evaluation of anthropometric parameters.*

Weight (mean, sd)	82.5 (11.9)	63.9 (6.1)	0.000
Height (mean, sd)	165.1 (5.5)	164.7 (5.7)	0.503
BMI (mean, sd)	30.2 (3.8)	23.49 (1.6)	0.000
Waist circumference (mean, sd)	111.4 (18.1)	78.4 (9.2)	0.000
Hip circumference (mean, sd)	118.5 (14.0)	103.2 (9.4)	0.000
WHR (mean, sd)	0.94 (0.01)	0.76 (0.04)	0.000

Table 3. — *Independent sample test: evaluation of age, BMI, HTN, diabetes, and low physical exercise in hyperplasia cases and in controls.*

	I n = 167	II n = 282	*p*
Age (mean, sd)	49.8 (3.0)	50.5 (3.2)	0.022
BMI (mean, sd)	30.2 (3.8)	23.49 (1.6)	0.000
HTN (n, %)	98 (58.7%)	59 (20.9%)	0.001
Diabetes (n, %)	25 (15.0%)	17 (6.0%)	0.002
Low physical exercise (n, %)	227 (81.5%)	45 (26.9%)	0.001

I: presence of endometrial hyperplasia; II: absence of endometrial hyperplasia.

Table 4. — *Indipendent risk factors for adenomatous hyperplasia (n = 449).*

		Confidence interval 95% CI		*p* value for odds ratio 2*1-sided
Variable	Odds Ratio	Lower	Upper	*p* value
Age	0.946	0.816	1.098	0.467
BMI	6.432	3.927	10.536	0.000
HTN	3.192	1.201	8.489	0.020
Diabetes	0.275	0.004	19.680	0.553
Physical activity	1.377	0.503	3.774	0.533

A diabetes diagnosis was assigned to the following diabetes registration criteria [16]: fasting plasma glucose (FPG) ≥ 126 mg / dl (7.0 mmol / l) and is defined as no caloric intake for at least eight hours. In the absence of unequivocal hyperglycemia, the authors confirmed diagnosis by repeat testing of evaluation of A1C (≥ 6.5%) or two-hour plasma glucose ≥ 200 mg / dl (11.1 mmol / l) during an oral glucose tolerance test (OGTT).

Diagnosis of HTN was assigned to those who met the following criteria: greater than or equal to two blood pressure measurements greater than 130 / 85 mm Hg in accordance with the rules to perform an accurate pressure measurement [17] or greater than or equal to one prescription for an anti-HTN drug. Patients were further subvided according to BMI values of < 30 kg / m^2 and ≥ 30 kg / m^2.

All patients described their physical activity according to the following parameters: 60 minutes or more three times a week, defined as "high" versus less than 60 minutes once a week or absence of physical activity, defined as "low".

Statistical analysis of data was performed. Data distribution was assessed with the independent sample test and all variables displayed a non-normal distribution. Descriptive statistics was assessed by calculating frequencies, medians, and ranges.

Multivariable logistic regression was performed to verify the presence of statistically significant correlation among age, HTN, BMI > 30 kg / m^2, diabetes, low physical activities (independent variables), and the presence of uterine hyperplasia.

Pearson's linear correlation coefficients were calculated to evaluate the relationship between BMI and leptin levels and significance was checked with Student's t-test. Significance was set at *p* less than 0.5.

Results

The age of patients ranged from 40 to 55 years (mean 48.2 years). From a total of 485 eligible women, 203 (41.8%) patients had an abnormal sonography pattern: in 167 (34.4%) the samples obtained with biopsy during hysteroscopy showed simple hyperplasia; two (0.4%) were endometrial carcinoma; five (1%) were hyperplasia with atypia and 29 (6%) were complex hyperplasia. Excluding the samples of carcinoma, complex and atypic hyperplasia, and depending on the results of histology, patients were allocated to one of two groups: group I (n = 167) simple hyperplasia and group II (n = 282) control patients with normal endometrium.

Patients were subvided according to BMI values of < 30 kg / m^2 and ≥ 30 kg / m^2. A positive correlation was noted between the concentration of leptin in serum and BMI; the concentration of leptin in group I patients with BMI < 30 was 7.8 ng / ml, as opposed to 3.2 ng / ml in the respective controls. For BMI ≥ 30 leptin concentrations in patients with or without endometrial hyperplasia were 13.5 ng / ml versus 7.8 ng / ml ($p < 0.005$). Mean plasma leptin level was 8.6 ± 4.8 ng/ml and the range was 1.7 to 29.6 ng / ml (Table 1).

The median age of women with hyperplasia was 49.8 years; in those with normal endometrium, the median age was 50.5 years (range 40 - 55 years). 98 (58.7%) patients with hyperplasia had HTN. In the group of patients that had hyperplasia, 25 (15.0%) were diabetic; 227 (81.5%) patients with hyperplasia practiced low physical activity (Table 2).

BMI and weight were higher in hyperplasia cases than in controls (82.5 vs 63.9) and waist and hip circumference and WHR was higher too (Table 3).

Age, BMI, hypertension, diabetes, and low physical exercise were considered to be independent risk factors for endometrial hyperplasia in women with abnormal bleeding.

When performing multivariable logistic regression, all independent variables lost their statistical significance (Table 4) except for BMI odds ratio (OR) 6.43, 95% CI 3.97 - 10.53, $p = 000$) and HTN (OR 3.19. 95% CI 1.20 - 8.48 $p = 0.020$).

Both were significantly associated with the presence of endometrial hyperplasia.

Discussion

This study has reported a rate for endometrial hyperplasia in premenopausal women with abnormal menstrual bleeding sufficient to warrant endometrial sampling. In the present study the incidence of adenomatous hyperplasia decreased with increasing age. Adenomatous hyperplasia was most frequent before 55 years of age, preceding the peak incidence of endometrial carcinoma by more than 10 years.

In this study, endometrial hyperplasia prevalence was approximately 34% of patients investigated by biopsy. It unusual to find 34% of premenopausal women with AUB or with abnormal sonography patterns diagnosed with endometrial hyperplasia. This is significantly higher than other previous estimates even if authors as Anastasiadis PG *et al*. disclose an endometrial hyperplasia prevalence of approximately 20% of patients investigated by biopsy for abnormal bleeding [18]. Taddei Gl *et al*. [19, 20] found in a study with 1,075 patients with AUB, a prevalence of endometrial hyperplasia of 20.2%, while 9.2% of patients were diagnosed with carcinoma. In the same study, taking into account only postmenopausal patients, hyperplasia represented 23.4%, with the prevalence of endometrial carcinoma increased to 12.3%. The analysis of the 203 cases of endometrial hyperplasia showed a clear predominance of cases with hyperplasia without atypia (167 cases), compared with cases with complex hyperplasia with (five cases) and without atypia (29 cases).

The present data showed that body weight, BMI, and WHR were higher in perimenopausal women with endometrial hyperplasia than in population controls. In particular the authors evaluated obesity, not only using weight, but also measuring waist circumference, hip circumference, WHR, and BMI. The obesity was present in a large percentage of the examined patients in this study. Obesity could lead to the development of endometrial hyperplasia by increasing the concentration of circulating estrogens and thus stimulation of growth of the endometrium. This could occur in several ways: by decreasing levels of circulating sex hormone-binding globulin [21] or by increasing the conversion of androstenedione to estrone that occurs with increased adipose tissue [22]. Premenopausal women who are obese could be at additional risk, since they are more likely to have periods of anovulation and therefore lower progesterone levels [23, 24], which increases their risk of endometrial proliferation and inadequate menstrual shedding of the endometrium. It is an emerging disease, characterized by increased peripheral aromatization of androgens to estrogens in adipose tissue and seems to be associated with an estrogenic state. However, the association between adenomatous hyperplasia and WHR disappeared after adjustment for BMI. This indicates that the quantity, but not the location of body fat is a risk factor for adenomatous hyperplasia. Other studies suggested that higher BMI is associated with endometrial hyperplasia as compared to women with lower BMI [20, 25].

Systemic HTN was present in 98 (58.7%) cases and in 59 (20.9%) controls of the examined patients of this study. Hypertension, especially associated with obesity, appears to be an important factor that may play a role in the pathogenesis of endometrial hyperplasia, Vorgias *et al*. found that hyperplasia with or without atypia occurs in approximately 50% of hypertensive women [26]. Moreover, it is known that systolic pressure and the prevalence of HTN increase dramatically with age.

Diabetes was present in 25 (15.0%) cases and in 17 (6.0%) controls of the patients included in this study. Although diabetes seems to be linked to endometrial hyperplasia even if there is only a study on rats [27], but BMI and nulliparity seem to be directly linked to endometrial hyperplasia [28].

In this study when performing multivariable logistic regression, only two independent variables had statistical significance. These data are in accordance with the international literature that indicates that the likelihood of hyperplasia is related to age and hormonal status [28]. These data could also be explained by the strict association between aging and climactery. Indeed, during the perimenopausal years, which are characterized by the endometrium's prolonged exposure to both estrogens and low progesterone levels, the unopposed estrogens may contribute to the pathogenesis of endometrial hyperplasia.

Furthermore th authors found that serum concentration of leptin in simple endometrial hyperplasia was higher than in controls with normal endometrium. The authors evaluated a positive correlation between leptin levels in serum and BMI. Other studies showed this correlation, but they analized the serum concentration of leptin in patients with endometrial cancer. Petridou *et al*. studied 84 women with endometrial cancer and 84 controls and they noted higher leptin levels in cancer patients and their correlation with BMI [29]. Cymbaluk *et al*. found similar data in their study, in particular they analized leptin levels in patients with endometrial cancer and with endometrial hyperplasia with atypia [30].

In conclusion, this study leads the authors to reconsider the influence of age, diabetes, HTN, BMI, physical activity on the development of endometrial hyperplasia, and highlights the need to find a clear relationship between experimental and epidemiologic features on the growth of endometrium.

The authors have also added evidence that leptin may be involved in hyperplasia as in other proliferative processes of the endometrium. Yuan *et al*. showed the expression of leptin receptors in endometrial cancer cells and found higher level of leptin in serum [31]. It is higher in obese women and the authors found that the risk factors statistically significant in this study for endometrial hyperplasia were BMI $\geq$ 30 kg / m^2 and HTN.

Increased level of leptin in obesity can be also considered as a marker of developing insulin resistance [32] by reducing tissue sensitivity to insulin, it is responsible for hyperinsulinemia, and it is the cause of elevated levels of free fatty acids. Leptin is also associated to high blood

pressure and high level of triglycerides [33]. The role of leptin should be studied as a possible independent risk factor for adenomatous hyperplasia.

A limit of this study is that the distribution of hormone-related characteristics in such a group almost certainly would not reflect that of women in general. Another limit of this study is that BMI, glucose levels, and blood pressure were examined as dichotomous variables. Future large prospective studies, considering such risk factors in a continuous model, may more powerfully identify age as the key factor in hyperplasia development and definitively exclude a relationship between other variables and endometrium growth.

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