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Markers of insulin resistance in perimenopausal women with endometrial pathology

Wskaźniki insulinooporności u kobiet z patologią endometrium w wieku okołomenopauzalnym

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Abstract

Objectives: *To determine and compare the prevalence of insulin resistance and carbohydrate metabolism parameters in women with endometrial pathology.*

Material and Methods: *100 perimenopausal women with abnormal uterine bleeding and/or abnormal endometrium were included into the study. Hysteroscopy with biopsy was performed. The study population was divided into four groups according to histopathological results of the endometrium: non-atypical endometrial hyperplasia, endometrial polyp, endometrial cancer, and controls. Fasting glucose and insulin levels and OGTT, IR indexes, occurrence of diabetes, pre-diabetic state, overweight, obesity, and hypertension were assessed.*

Results: *Insulin resistance was diagnosed in 41.0% of the patients. The prevalence of markers of insulin resistance increased to 57.1% in cases with confirmed endometrial pathology, compared to 31.8% in histologically normal endometrium ($p<0.01$). The frequency of insulin resistance was 52.6% ($p=0.059$) and 55.5% ($p=0.04$), respectively, in women with non-atypical hyperplasia and patients with endometrial polyps when compared to the control group. Abnormal parameters of carbohydrate metabolism indicate little sensitivity and specificity in predicting endometrial hyperplastic lesions. The insulin levels at 120 minutes of OGTT correlate best with such changes (concentration >57 μU/ml in case of hyperplasia and >61 μU/ml in endometrial polyps).*

Conclusion: *Insulin resistance and carbohydrate metabolism disturbances are common in women with endometrial pathologies. In these patients there is clinical basis for recommending lifestyle modification (change of diet, more physical activity), or for introduction of pharmaceutical insulin-sensitizing agents.*

Key words: **endometrial polyp** / **non-atypical endometrial hyperplasia** / / **endometrial cancer** / **insulin resistance** /

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Streszczenie

Cel pracy: *Ocena częstości występowania insulinooporności oraz zaburzeń węglowodanowych u kobiet z patologią endometrium.*

Materiał i metody: *100 pacjentek w wieku okołomenopauzalnym z patologicznymi krwawieniami z dróg rodnych i/lub poszerzonym endometrium w badaniu USG TV. U każdej pacjentki przeprowadzono badanie histeroskopowe z biopsją endometrium. Na podstawie oceny histopatologicznej endometrium badaną populację podzielono na 4 grupy pacjentek (rozrost endometrium bez atypii, polip endometrialny, rak endometrium, grupa kontrolna).*

U pacjentek oznaczono stężenia glukozy i insuliny na czczo oraz wykonano OGTT, określono wskaźniki insulinooporności, oceniono występowanie cukrzycy, stanu przedcukrzycowego, nadwagi, otyłości, nadciśnienia tętniczego.

Wyniki: *Insulinooporność stwierdzono u 41,0% pacjentek. Częstość nieprawidłowych markerów insulinooporności wzrasta do 57,1% w przypadkach histopatologicznie potwierdzonej patologii endometrium w porównaniu do 31,8% z prawidłowym endometrium (p<0,01). Częstość insulinooporności u kobiet z hiperplazją bez atypii wynosiła 52,6% (p=0,059 w stosunku do grupy kontrolnej), natomiast w przypadku pacjentek z polipem endometrialnym 55,5% (p=0,04 w stosunku do grupy kontrolnej). Nieprawidłowe parametry gospodarki węglowodanowej wykazują małą czułość i swoistość w przewidywaniu rozrostów endometrium. Najlepiej z tymi zmianami koreluje stężenie insuliny w 120. minucie testu OGTT (powyżej 57 µU/ml w przypadku hiperplazji i powyżej 61 µU/ml w przypadku polipów).*

Wnioski: *Insulinooporność i zaburzenia gospodarki węglowodanowej występują często u kobiet z patologią endometrium. U tych pacjentek istnieją kliniczne podstawy do zalecenia modyfikacji stylu życia (zmiana diety, zwiększenie aktywności fizycznej) lub stosowania farmakologicznych środków uwrażliwiających na insulinę.*

Słowa kluczowe: **hiperplazja endometrium bez atypii** / **polip endometrialny** / / **rak endometrium** / **insulinooporność** /

Introduction

Endometrial pathology represents a frequent finding in peri- and postmenopausal women admitted to out-patient gynecology departments. It is often found not only in cases with abnormal uterine bleedings, but also in obese women with hypertension and/or disturbed carbohydrate metabolism [1].

It is estimated that 60-70% of endometrial cancers develop due to endocrine-metabolic disorders [2, 3]. There is accumulating evidence that hyperinsulinemia is associated with carcinogenesis [4] and that hyperinsulinemia and insulin resistance are associated with a more aggressive course of endometrial cancer [2, 5].

Major modifiable determinants of insulin resistance, such as obesity and physical inactivity, have also been shown to constitute risk factors for endometrial cancer [6-8]. Excessive fat consumption and overweight are important risk factors present in almost 50% of women with endometrial cancer risk. In premenopausal women, overweight may lead to insulin resistance, ovarian androgen excess, anovulation and chronic progesterone deficiency. However, in postmenopausal women it causes higher circulating concentrations of bioavailable estrogens from extraglandular conversion of androgens. Higher levels of estrogens stimulate endometrial-cell proliferation, inhibit its apoptosis and promote angiogenesis [9]. A BMI above 25 kg/m² doubles a woman's risk of endometrial cancer, and a BMI above 30 kg/m² triples the risk [10].

Such endometrial lesions as atypical hyperplasia are strongly related to cancer development, whereas others like endometrial polyps or non-atypical hyperplasia are rather of benign nature with carcinogenesis not exceeding 1-3%. Nevertheless, all these endometrial changes represent different forms of endometrial proliferation [1].

Much has been said about the relationship between carbohydrate metabolism and endometrial cancer risk in peri- and postmenopausal women, but much less about the correlation between insulin resistance and endometrial polyps [2, 11, 12].

Objectives

To determine and compare the prevalence of insulin resistance and carbohydrate metabolism parameters in peri- and postmenopausal women submitted to hysteroscopic examination with endometrial biopsy due to suspected endometrial pathology.

Material and methods

100 peri- and postmenopausal women with abnormal uterine bleedings and/or abnormal endometrium on transvaginal ultrasound (>5mm in postmenopausal women and in still menstruating patients between 4-6 day of the cycle), admitted to the Department of Gynecological Endocrinology, Medical College, Jagiellonian University, Cracow, Poland between April 2007 and April 2008, underwent a hysteroscopic examination.

Diagnostic hysteroscopy was performed in each patient using a 'size 4' hysteroscope based on a 2.0 mm telescope (Karl Storz, Germany).

The hysteroscope is characterized by continuous-flow sheath with an oval profile and a total diameter of 4 mm. No anesthesia was required owing to the vaginoscopic approach (without speculum or tenaculum) by Bettocchi method. A 0.9% saline was used as distention medium.

Patients with endometrial polyps diagnosed by hysteroscopy were referred for hysteroscopic polyp resection with subsequent curettage in a surgical setting under general anesthesia. The remaining patients (without endometrial polyp) were qualified for

subsequent dilation & curettage under general anesthesia in order to obtain specimens for histopathological examination.

The material from both procedures was sent to the Department of Pathomorphology of Medical College, Jagiellonian University, Cracow, for histopathological examination.

In each patient the oral glucose tolerance test (OGTT) was assessed – glucose and insulin levels (fasting, 60 and 120 minutes after a 75g glucose load).

Demographic characteristics and data on diabetes, hypertension and menopausal status were collected, and anthropometric parameters were analyzed. Women were considered postmenopausal when there had been at least 12 consecutive months of amenorrhea [13]. Overweight was defined as BMI between 25-29.9, obesity when BMI ≥30 [14].

Diabetes was diagnosed according to the American Diabetes Association recommendations (fasting glucose ≥ 7.0 mmol/l (2 measurements) and/or 120' post-load glucose in OGTT ≥ 11.1 mmol/l) [17]. Prediabetes was defined as impaired fasting glucose (IFG) – fasting glucose 5.6-6.9 mmol/l and/or impaired glucose tolerance (IGT) – 120' post-load glucose in OGTT 7.8-11.0 mmol/l [15].

The formula described by Matthews et al.: fasting glucose [mmol/L] × fasting insulin [μU/mL])/22.5 was used for HOMA index [16].

Local ethical committee approval was obtained for the trial.

In the paper several statistical tests were used. Proportion tests were used to check the significance of differences between the frequency of symptoms observed in the groups of patients. The strength of the relationship between the variables like glucose levels, insulin levels, HOMA index and age was estimated by non-parametric correlation analysis (Spearman). Mann-Whitney and Kruskal-Wallis tests were used to investigate the differences of mean values between the groups of patients. ROC curves were used to determine the cut-off points of the examined parameters for specific endometrial pathology and $p < 0.05$ was considered as statistically significant. The statistical analysis was performed with the use of a commercial software program – StatSoft, Inc. (2007) STATISTICA (data analysis software system), version 8.0. www.statsoft.com.

Results

Out of 100 women included into the study, four groups of patients were selected according to the result of the histopathological examination:

- non-atypical endometrial hyperplasia (NAH) – n=21 (20 hyperplasia simplex, 1 hyperplasia complex),
- endometrial polyps (EP) – n=23,
- endometrioid endometrial cancer (EC) – n=8,
- histopathologically normal endometrium – the control group (C) – n=48.

Tables I and II show patient characteristics with regard to the measured parameters.

Patients with endometrial polyps and endometrial cancer were significantly older than patients with endometrial hyperplasia and controls (respectively, 57.87±9.23 yrs and 67.0±6.97 yrs vs. 49.90 ±4.48 yrs and 52.48 ±5.18 yrs) (Table I).

Patients in all 4 groups did not differ in weight and BMI but, importantly, the majority of patients in each group (62.5% – 75%) were classified either as obese or overweight (Table I, Table II).

There was no significant difference in the occurrence of hypertension, prediabetes, prediabetes + diabetes, obesity, overweight, obesity + overweight between the groups. Type 2 diabetes occurred more frequently in patients with EC (25%) and EP (17.39%) than in controls (2.08%). Nevertheless, it is necessary to mention that although these results were statistically significant, the number of the patients with type 2 DM was very small (4 patients in the EP and 2 in the EC groups) (Table II).

OGTT test results demonstrated differences in mean serum fasting glucose levels between the EP (5.74±1.21) or EC (5.89±0.75) and the control group (5.07±0.59) (Tab. III). These differences were probably related to the age difference between the groups due to the significant correlation between age and glucose levels ($r=0.302$; $p<0.05$) in the examined population (Tab. IV). Significant differences in mean insulin levels at 60 minutes after the glucose load between NAH, EP and the control group (104.15±76.63 and 133.50±177.8 vs. 69.17 ±43.97) were found (Tab.III). Importantly, no correlation between insulin levels and patient age was found (Table IV).

HOMA index was higher in the EP group when compared to the control group (3.79±2.69 vs. 2.27±1.93) (Table V). Due to the fact that patients with EP were older than controls, the correlation between age and HOMA in the examined population was checked. No correlation between the parameters was found (Table IV).

Prevalence of at least one of insulin resistance markers (insulin 0' > 12μU/ml, insulin 120' > 100μU/ml, HOMA ≥ 2.6,) was seen more often in patients with EC and EP comparing to the control group (80% and 55.55%, respectively vs. 31.81%). Prevalence of one of these markers was observed in 52.63% of the women with endometrial hyperplasia, but in that case the difference did not reach statistical significance. Increased fasting insulin levels > 12μU/ml occurred significantly more often in the EC patients when compared to the control group (80% vs. 25%). Increased insulin levels at 120 minutes after a 75g glucose load (above 100μU/ml) occurred more frequently in NAH patients than in controls (33.33% vs. 9.09%). HOMA index ≥ 2.6 was observed more often in EC and EP patients compared to the control group (respectively, 80% and 55.56% vs. 29.55%) (Table VI).

ROC curves were implemented to check if there were any cut-off points, above which the endometrial pathology can be seen more often. In case of insulin levels 60 minutes after the glucose load, ROC curve showed discrimination ability between the NAH group and the control group for value 62.7 μU/ml with sensitivity 76.5% and specificity 55% (Fig. 1). 45.0% of controls and 76.47% of the NAH patients had serum insulin 60' levels 62.7 μU/ml (p=0.030).

In case of insulin levels at 120 minutes after the glucose load, the ROC curve showed discrimination ability between the NAH group and the control group for value 57.3 μU/ml with sensitivity 61.1% and specificity 77.3% (Fig. 2). 22.73% of controls and 88.89% of the NAH patients had serum insulin 120' levels 57.3 μU/ml (p=0,004).

Moreover, in case of insulin levels at 120 minutes after the glucose load, the ROC curve showed discrimination ability between the EP group and the control group for value 61.2 μU/ml with sensitivity 55.5% and specificity 77.3% (Fig.3). 22.73% of controls and 55.56% of the EP patients had serum insulin 120' levels 61.2 μU/ml (p=0.004).

Table I. Group characteristics (mean values with standard deviations) .

	Controls n=48	Hyperplasia n=21	Polyp n=23	Cancer n=8	Statistic significance (p)
Age [years]	52,48 ±5,18	49,90 ±4,48	57,87 ±9,28	67,0 ±6,97	NAH/EP**; NAH/EC*** C/EC***; C/EP**; EC/EP*
Weight [kg]	75,38 ±15,20	73,90 ±15,36	77,53 ±13,05	79,0 ±20,15	ns
BMI [kg/m^2]	29,02 ±5,20	27,63 ±6,16	29,05 ±3,92	29,29 ±7,92	ns

**p<0,05; **p<0,01; ***p<0,001; ns – statistically nonsignificant*
NAH – non-atypical hyperplasia; C – control group; EP – endometrial polyp; EC – endometrial cancer

Table II. Clinical characteristics of examined groups of patients.

	Controls n=48	Hyperplasia n=21	Polyp n=23	Cancer n=8	Statistic significance (p)
Postmenopausal	47,92%	38,10%	65,22%	100%	C/EC**; EC/NAH**; EC/EP*;
Hypertension	52,08%	42,86%	47,83%	62,50%	ns
Diabetes t.2 (DM)	2,08% (1/48)	9,52% (2/21)	17,39% (4/23)	25% (2/8)	C/EC**; C/EP*
Prediabetes (Pr)	31,25%	33,33%	30,43%	25%	ns
DM+Pr	33,33%	42,86%	47,83%	50%	ns
Obesity (O)	43,75%	33,33%	47,83%	37,50%	ns
Overweight (N)	31,25%	38,10%	21,74%	25%	ns
O+N	75%	71,43%	69,57%	62,50%	ns

**p<0,05; **p<0,01; ***p<0,001; ns – statistically nonsignificant*
NAH – non-atypical hyperplasia; C – control group; EP – endometrial polyp; EC – endometrial cancer

Table III. Glucose and insulin levels – fasting and in OGTT (mean values with standard deviations).

	Controls n=48	Hyperplasia n=21	Polyp n=23	Cancer n=8	p
Glucose 0' [mmol/l]	5,07 ±0,59	5,39 ±0,69	5,74 ±1,21	5,89 ±0,75	C/EP*; C/EC*
Glucose 60' [mmol/l]	7,96 ±2,56	9,24 ±3,30	8,57 ±3,18	9,70 ±3,49	ns
Glucose 120' [mmol/l]	6,28 ±1,83	6,53 ±2,44	7,41 ±3,15	8,28 ±3,32	C/EC*
Insulin 0' [µU/ml]	9,73 ±7,44	11,45 ±7,04	13,73 ±8,31	13,82 ±5,07	ns
Insulin 60' [µU/ml]	69,17 ±43,97	104,15 ±76,63	133,50 ±177,58	71,58 ±26,03	C/NAH*; C/EP*
Insulin 120' [µU/ml]	50,24 ±36,88	70,26 ±46,44	59,26 ±32,55	77,92 ±51,97	ns

p- statistic significance
**p<0,05; **p<0,01; ***p<0,001; ns – statistically nonsignificant*
NAH – non-atypical hyperplasia; C – control group; EP – endometrial polyp; EC – endometrial cancer
Glucose 0'/Insulin 0' – fasting glucose/insulin
Glucose 60'/Insulin 60' – glucose/insulin 60 minutes after glucose load (75g)
Glucose 120'/Insulin 120' – glucose/insulin 120 minutes after glucose load (75g)

Table IV. Correlation between age and examined parameters within examined population. Współzależność wieku z wybranymi parametrami w całym materiale.

Correlated parameters		R	Significance of correlation ratio	Correlation
Age	HOMA-IR	0,212	p=0,070	no correlation
Age	QUICKI	0,143	p=0,193	no correlation
Age	Glucose 0'	0,302	p=0,003	weak positive correlation
Age	Glucose 60'	0,332	p=0,004	weak positive correlation
Age	Glucose 120'	0,280	p=0,009	weak positive correlation
Age	Insulin 0'	0,159	p=0,147	no correlation
Age	Insulin 60'	0,079	p=0,504	no correlation
Age	Insulin 120'	0,121	p=0,269	no correlation

R – Pearson correlation ratio

Table V. Mean HOMA and QUICKI in examined groups of patients (mean values with standard deviations). Średnie wartości HOMA i QUICKI w poszczególnych grupach pacjentek (średnie wartości oznaczeń z odchyleniami standardowymi)

	Controls n=48	Hyperplasia n=21	Polyp n=23	Cancer n=8	(p)
HOMA	2,27 ±1,93	2,73 ±2,26	3,79 ±2,69	3,78 ±1,59	C/EP*;
QUICKI	0,65 ±0,14	0,60 ±0,10	0,58 ±0,12	0,54 ±0,07	ns

**p<0,05; **p<0,01; ***p<0,001; ns – statistically nonsignificant*
NAH – non-atypical hyperplasia; C – control group; EP – endometrial polyp; EC – endometrial cancer

Table VI. Frequency of selected insulin resistance markers in examined groups of patients Częstość występowania wybranych markerów insulinooporności w poszczególnych grupach pacjentek

	Controls n=48	Hyperplasia n=21	Polyp n=23	Cancer n=8	(p)
Insulin 0' >12 μU/ml (A)	25%	33,33%	44,44%	80%	C/EC*
Insulin 120' >100 μU/ml (B)	9,09%	33,33%	11,11%	20,0%	C/NAH*
HOMA ≥2,6 (C)	29,55%	38,89%	55,56%	80%	C/EC*; EP/C*
AvBvC	31,81%	52,63%	55,55%	80%	C/EP*; C/EC*

**p<0,05; **p<0,01; ***p<0,001; ns – nieistotne statystycznie*
NAH – non-atypical hyperplasia; C – control group; EP – endometrial polyp; EC – endometrial cancer
Insulin 0' – fasting insulin, Insulin 120' – insulin 120 minutes after glucose load (75g)

Discussion

Histologically, endometrial carcinomas have been classified into endometrioid (type I) and non-endometrioid types (type II). Type I tumors account for 80% of endometrial cancers, and are generally associated with endometrial hyperplasia [12]. The theory describing the relationship between endogenous steroid hormones and endometrial cancer risk is known as the unopposed estrogen hypothesis [17]. This hypothesis proposes that endometrial cancer risk is increased in women who have high plasma bioavailable estrogens and/or low plasma progesterone, so that mitogenic effects of estrogens are insufficiently counterbalanced by progesterone [12].

There is evidence suggesting that endometrial neoplasia before menopause is related especially to progesterone deficiency, as we can observe in women with chronic anovulatory cycles like in the polycystic ovary syndrome, while after the menopause the cancer risk is directly related to estrogen levels [17, 18].

Endometrial hyperplasia, an overgrowth or thickening of the uterine lining, can be the first warning sign of a pathological process, eventually leading to endometrial carcinoma [19]. The majority of endometrial hyperplasia cases regress spontaneously [20]. In the case of non-atypical simple endometrial hyperplasia, only 1% progresses to carcinoma. Atypical complex endometrial hyperplasia, the lesion with the highest neoplastic potential,

progresses to carcinoma in 29% of patients [21]. Risk factors for endometrial hyperplasia are similar to those found to be associated with endometrial cancer. Obesity is a predominant risk factor for endometrial hyperplasia in younger women [22]. A recent study concluded that high education, obesity, diabetes and hormone replacement therapy increase the risk of endometrial hyperplasia [23].

Endometrial polyps are benign overgrowths of endometrial tissue containing endometrial glands in a fibrous stroma [24]. Endometrial polyps are very common. Studies reported that they can be found in approximately 24-25% of the general female population [25]. Polyps occur most commonly in women between the ages of 40 and 50 years [24, 26]. Increasing age is associated with an increased risk that polyps are premalignant or malignant [27]. Studies report an incidence of malignancy from 0.42% to 3.2% within endometrial polyps, with most studies recording an incidence around 1% [28, 29].

The etiology of endometrial polyps remains unclear. Three central causes of endometrial polyps have been suggested:

- Polyps are local outgrowths of the basalis endometrium – because basalis cells respond to estrogen, but not progesterone, polyps are stimulated to undergo hyperplasia, but could be resistant to the antiproliferative effects of progesterone.
- Polyps form in response to an imbalance of estrogen and progesterone receptors.
- Polyps are a product of genetic mutations that increase mitosis and decrease apoptosis [25].

Several risk factors predispose women to developing endometrial polyps. Age, obesity, hypertension, tamoxifen, hormone replacement therapy, anovulation, endometriosis and age at menopause have all been associated with polyp occurrence. Many of these risk factors are associated with elevated estrogen levels. It was hypothesized that estrogens lead to the production of certain growth factors, which may promote polyp growth [30]. Some studies have tried to find an association between diabetes mellitus and endometrial polyps growth, but so far they have not confirmed the influence [31, 32]. A clinically important fact is that 13-50% of women with abnormal uterine bleedings have polyps [33]. Polyps account for approximately 30% of postmenopausal bleeding [34].

Although the chance of malignancy in case of non-atypical endometrial hyperplasia or endometrial polyps is very low, evaluation of these pathologies is still important as they are frequent findings in gynecological practice and require further diagnostic steps. When abnormal uterine bleeding is present, the older the patient, the higher the suspicion for endometrial pathology. While premenopausal bleedings can be managed conservatively, any uterine bleeding after menopause must be investigated expeditiously as the risk of endometrial cancer is higher in that age group [1].

Endometrial cancer has high incidence rates in the Western, industrially developed societies. In these countries, obesity has been associated with 2-to 5-fold increase in endometrial cancer risk in both pre- and postmenopausal women and has been estimated to account for about 40% of endometrial cancer cases. Apart from excess weight, epidemiological evidence suggests that lack of regular physical activity may also be a risk factor. A major metabolic link between obesity, lack of physical

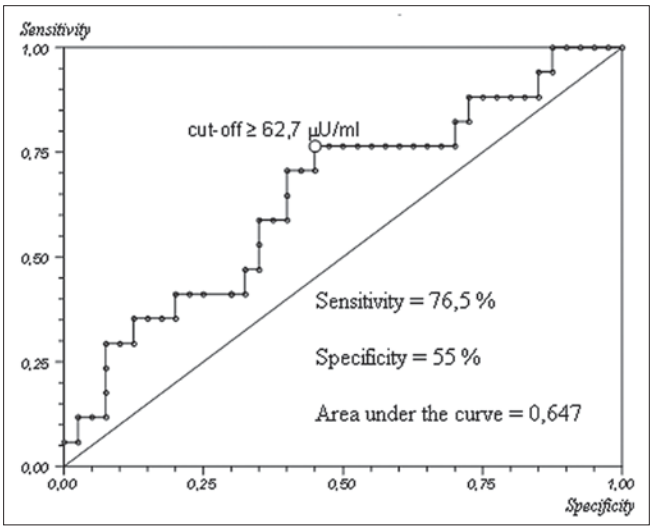

Figure 1. ROC curve for insulin 60' – NAH vs Controls.

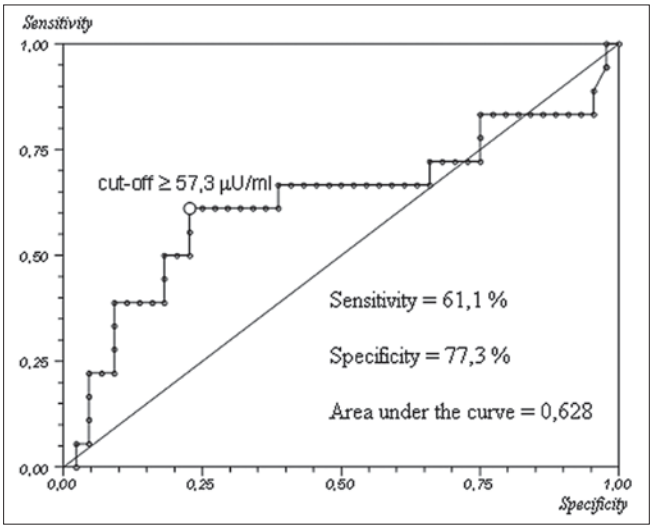

Figure 2. ROC curve for insulin 120' – NAH vs Controls.

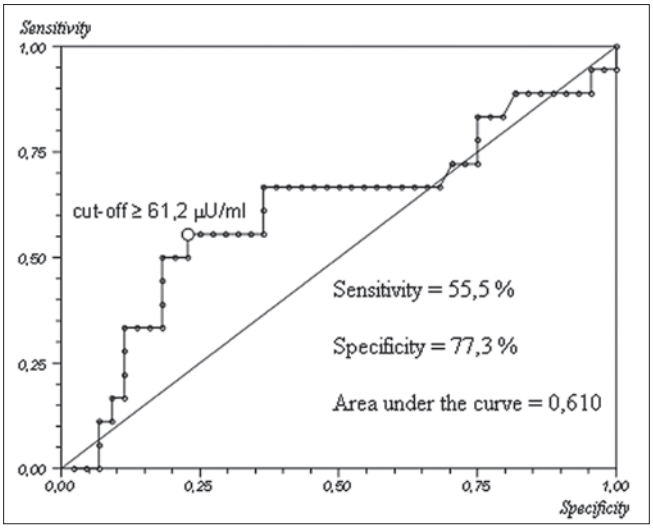

Figure 3. ROC curve for insulin 120' – Polyp vs Controls.

activity and development of ovarian androgen excess is chronic hyperinsulinemia. Obesity and physical inactivity lead to insulin resistance, and increased fasting and non-fasting insulin levels [35,36]. Other conditions characterized by insulin resistance and hyperinsulinemia, such as noninsulin-dependent diabetes mellitus and polycystic ovary syndrome (PCOS), have also been related to an increased endometrial cancer risk [12, 37].

Insulin has been shown to promote the growth of cancer cell lines in vitro, including endometrial cancer cells [38]. Also, the role of insulin in pathogenesis of endometrial cancer was shown in several case-control studies. It has been observed that elevated levels of C-peptide (a marker of pancreatic insulin secretion) were related to an increase in endometrial cancer risk [18, 39]. Other studies showed higher fasting and post-glucose challenge insulin in endometrial cancer patients than in control groups [40-42].

Insulin, as the agent playing a role in pathogenesis of endometrial cancer, may act through various mechanisms:

- Insulin can act as a growth factor, it can stimulate cell proliferation and inhibit apoptosis directly through insulin receptors [38].
- Insulin may increase IGF-I bioactivity in many tissues, including the endometrium, by down-regulating the synthesis of IGFBP-1 [43, 44].
- In postmenopausal women insulin induces inhibition of hepatic synthesis of sex hormone-binding globulin (SHBG), which results in an increase in the free estradiol levels [45-47].
- In premenopausal women chronically elevated insulin concentrations contribute to ovarian androgen excess, which may cause chronic anovulation and progesterone deficiency [12].

In the present study abnormal markers of insulin resistance (fasting insulin levels >12 μU/ml, insulin at 120 minutes of OGTT >100 μU/ml, HOMA index ≥2.6) were found in 57.1% of women with histopathologically confirmed endometrial pathology when compared to 31.8% with histologically normal endometrium ($p<0.01$). The frequency of abnormal markers of insulin resistance in women with non-atypical hyperplasia was 52.6% ($p=0.059$ compared to the control group), whereas in case of patients with endometrial polyps it was 55.5% ($p=0.04$ compared to the control group).

Interestingly, in the presented study there is relatively high percentage of insulin resistance in women with histopathologically normal endometrium (31.8%). According to data of the European Group for the study of Insulin Resistance from 1999, the prevalence of insulin resistance in European Caucasian population was estimated at 16% [48]. Higher proportion observed in the conducted study is most probably the result of prior selection of women, characterized by abnormal uterine bleedings and/or abnormal transvaginal ultrasound image.

Elevated fasting insulin levels (>12 μU/ml) were noticed in approx. 44% of patients with polyps and 33% of patients with hyperplasia, but these results were not significant comparing to the control group (25%).

Elevated levels of insulin at 120 minutes of OGTT (>100 μU/ml) were noticed in approx. 33% of patients with hyperplasia, which reached statistical significance when compared to the control group (9.09%).

Elevated HOMA index of (≥2.6) was noticed in approx. 39% of cases with non-atypical hyperplasia (ns) and 56% of cases with endometrial polyps, and in that last case it reached statistical significance when compared to controls (29.55%). Moreover, mean values of HOMA index were significantly higher in case of patients with endometrial polyps than in the control group. Women with endometrial polyps were significantly older than controls, but Pearson correlation within the whole examined population did not show correlation of this index with age. Moreover, according to one of the recent studies, age per se does not influence insulin sensitivity. Insulin resistance, often observed in the elderly, results most probably from obesity and lack of physical activity. On the other hand, insulin secretion, which is dependent on age, decreases 0.7% per year in people with normal glucose tolerance, while in people with impaired tolerance this percentage is twice as high [49].

In our study, 2 out of 21 patients with non-atypical endometrial hyperplasia were diagnosed with type 2 diabetes mellitus. What is interesting, frequent occurrence of this disease was observed not only in patients with endometrial cancer, but also with endometrial polyps. Nevertheless, as previous studies on large groups of patients did not show a connection between DM and endometrial polyp pathogenesis [31,50], and in our study DM was diagnosed only in 4 patients with endometrial polyp, we should be careful when drawing conclusions. We did not observe any significant differences in the body mass index (BMI) among the four groups of patients, but the mean values of BMI in all groups corresponded to excessed body weight.

Mean plasma glucose levels were higher in patients with endometrial cancer and endometrial polyps, and the highest in the endometrial cancer patients at 120 minutes after the glucose load. However, because of more advanced age of women in both mentioned groups, these results cannot be taken into account. The literature reports that glucose tolerance decreases with age [49], and in our study weak, but positive correlation between glucose concentration and age was indeed observed.

Importantly, no correlation between insulin levels and patient age was found. Significant difference in mean serum insulin levels at 60 minutes after the glucose load between EP, NAH and the control group was found.

Based on the ROC curve, the levels of insulin at 120 minutes of OGTT proved to be the most useful marker for predicting endometrial pathology. In case of levels exceeding 57-61 μU/ml, we can expect a higher risk of hyperplasia or endometrial polyps (with sensitivity of 55.5-61.1 % and specificity of 77.3%, p 0.004 and 0.012, respectively).

The analysis of the ROC curves proved also that insulin levels at 60 minutes of OGTT can be a predictor of endometrial hyperplasia. In case of insulin levels ≥62.7 μU/ml, measured one hour after the glucose intake, a higher risk of this type of endometrial pathology can be expected (with sensitivity of 76.5% and specificity of 55%, $p=0.03$).

Based on the conducted study, as well as the above mentioned literature, it can be concluded that hyperinsulinemia and insulin resistance are commonly found in women with endometrial hyperplasia. However, interestingly, in our study insulin resistance markers were seen frequently also in patients with endometrial polyps. On the basis of the obtained results we could hypothesize that insulin can play a role not only in the pathogenesis of endometrial hyperplasia and endometrial cancer,

but also endometrial polyps. Possibly, the same mechanisms of insulin action which are responsible for promoting the growth of cancer cells play a role in the pathogenesis of endometrial polyps.

Conclusions

Insulin resistance and carbohydrate metabolism disturbances are common in women with endometrial pathology. In case of women with abnormal insulin resistance markers, who experience pathological uterine bleeding and/or abnormal endometrium in transvaginal ultrasound, there is clinical basis for recommending modification of life style (change of diet, more physical activity), or introduction of pharmaceutical insulin-sensitizing agents, which additionally can have anti-proliferative effect on the endometrium. Nevertheless, more studies on that subject are needed.

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