Expression of hormone receptors, Bcl-2, Cox-2 and Ki67 in benign endometrial polyps and their association with obesity

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Abstract. The present study examined the immunoexpression of the estrogen receptor (ER), the progesterone receptor (PR), B-cell lymphoma 2 (Bcl-2), cyclooxygenase-2 (Cox-2) and Ki67 in endometrial polyps and their association with obesity. In total, 515 premenopausal and postmenopausal females undergoing hysteroscopy with histological diagnosis of benign polyps were included. The immunohistochemical expression of the ER, PR, Bcl-2, Cox-2 and Ki67 was compared between obese and non-obese females. The median final score demonstrated a higher PR expression in the stromal and glandular compartments of postmenopausal obese females as compared with no-obese females. However, in this group, there was no difference in regard to the ER. No difference in hormone receptor expression was identified among premenopausal females. In postmenopausal females, the immunoexpression of Cox-2 and Bcl-2 in the glandular epithelium was higher in obese than in non-obese females. Among premenopausal females, obese females demonstrated a higher Bcl-2 expression in the glandular epithelium than non-obese females. There were no differences in Ki67 expression between obese and non-obese females. Polyps from obese females had a higher PR expression in the glandular and stromal compartments. The expression of Cox-2 and Bcl-2 was higher in the glandular compartment. These data suggested that the etiology and pathogenesis of polyps in obese females appear to be associated with the PR, the inhibition of apoptosis and cellular mechanisms linked with inflammation.

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Abbreviations: ER, estrogen receptor; PR, progesterone receptor

Key words: estrogen receptor, progesterone receptor, Bcl-2, Cox-2, Ki67, endometrial polyps, obesity

Introduction

Obesity is currently a worldwide public health problem. In females, obesity increases mainly during the late menopausal transition (1,2). Weight gain is a risk factor for various comorbid conditions, including endometrial pathology (3).

The incidence of endometrial polyps in the general female population ranges from 7.8 to 34.9%, depending on the population studied. Polyps are most commonly identified during menopausal transition (4-6). The etiology and pathogenesis of polyps remain to be fully elucidated. However, it is hypothesized that the presence of hormone receptors is directly associated with the pathophysiology of endometrial polyps (7). Obesity has been identified as a risk factor for endometrial polyp development (3,8-10), although little is known about the association between hormone receptors in polyps and obesity.

Studies using immunohistochemical techniques have identified high estrogen receptor (ER) and progesterone receptor (PR) expression levels in endometrial polyp tissue compared with the adjacent endometrium (11,12).

In addition to the effect of hormonal factors, endometrial polyps appear to have two integrated components: Proliferation and apoptosis. B-cell lymphoma 2 (Bcl-2) is considered an inhibitor of apoptosis and is important in the increased expression and consequential loss of apoptotic activity (12).

Ki-67, a marker of cell proliferation, is found in the proliferative phase of endometrial cells. High Ki-67 concentrations are also found in endometrial carcinomas (13). However, studies have demonstrated a very low Ki-67 expression in endometrial polyps (12,13).

Another factor possibly associated with endometrial polyp development is the enzyme cyclooxygenase-2 (Cox-2), which is not produced under normal conditions. The enzyme is only produced during inflammation, cell proliferation and differentiation (14). Cox-2 expression has been observed in hyperplasia and endometrial polyps, suggesting a possible role of prostaglandins in the pathogenesis of these lesions (15).

Increasing Cox-2 and Ki67 levels appear to be associated with obesity. In a study by Gao *et al* (16) a higher leptin concentration caused by obesity increased the production and action of Cox-2, which in turn increased angiogenesis and cell proliferation. This mechanism may also explain the higher frequency of endometrial polyps in obese females (16).

Obesity appears to be a risk factor not only for the development of polyps (9,10), but also for the possibility of malignancy in these lesions (17,18). The effect of body weight in the pathogenesis of polyps, its association with estrogen/progesterone and the processes of apoptosis, proliferation and inflammation, remain unclear and conflicting. Knowledge of the mechanisms involved in the development of uterine polyps may contribute to a better understanding of endometrial polyp formation and progression in obese females. The aim of the present study was to determine the expression of ER, PR, Bcl-2, Cox-2 and Ki67 in benign endometrial polyps in premenopausal and postmenopausal females and their association with obesity.

Materials and methods

Ethics statement. A cross-sectional study was conducted at the Women's Hospital of Professor Dr Jose Aristodemo Pinotti, CAISM/Unicamp School of Medicine (Campinas, Brazil) and approved by the Research Ethics Committee of the State University of Campinas (Campinas, Brazil), under number 092/2011.

Patients and samples. From January 1998 to December 2008, following hysteroscopic resection of the endometrium, pathologists at the Department of Pathology, Unicamp School of Medicine, (Campinas, Brazil) confirmed the diagnosis of polyps in 800 females. Tamoxifen users, current users of hormone replacement therapy and patients presenting with premalignant or malignant polyps were excluded from the present study. In total, 515 cases remained in the sample. Clinical, pathological and hysteroscopic data were retrieved from patient medical records. Age, postmenopausal bleeding, presence of hypertension, obesity and diabetes mellitus were the clinical features observed. Obesity was a condition defined as a body mass index (BMI) ≥30.

A gynecologist performed surgical hysteroscopy on the patients under spinal anesthesia. A 10 mm Karl Storz® monopolar electrosurgical endoscope (resectoscope) was used for the procedure and the distending medium was a 1.5% glycine solution.

Tissue microarray (TMA). TMA blocks were acquired by taking two 1 mm core samples for each case. Tissue sections from the TMA blocks were 5 μm thick. Deparaffinization was performed in an incubator for 24 h at 60˚C. Subsequently, the slides were washed in xylene at 60˚C for 20 min, xylene at room temperature for 20 min, 100% ethanol for 30 sec, 85% ethanol for 30 sec and then 70% ethanol for 30 sec. The slides were washed in distilled tap water.

Citrate buffer solution (10 mM; pH 6.0) was heated to the boil in a pressure cooker (Eterna®; Nigro, Araraquara, São Paulo, Brazil) without sealing the lid. The slides were immersed into boiling retrieval buffer and the cooker lid was sealed with the safety valve open. Following the release of saturated vapor, the safety valve was lowered until total pressurization. The lid of the cooker containing the slides was lifted and the slides were washed in distilled tap water.

Endogenous peroxidase activity was quenched by 3% hydrogen peroxide (H_2O_2; 10 volumes) and washed three times for 10 min each. The slides were rinsed in distilled tap water and 10 mM phosphate-buffered saline (PBS) for 5 min (pH 7.4).

The slides were incubated with primary antibody diluted in a predefined titer in 1% PBS containing bovine serum albumin (A9647; Sigma-Aldrich, St Louis, MO, USA) and 0.1% sodium azide for 18 h in a humidity chamber at 4˚C. Primary monoclonal antibodies against ER (dilution, 1:250; no. M7047; clone 1D5; Dako, Carpinteria, CA, USA), PR (dilution, 1:500, no. M3569; clone PgR 636; Dako), Bcl-2 (dilution, 1:200; no. M887; Biogen Idec, Weston, MA, USA) and Ki-67 (dilution 1:1,000; no. M7240; clone MIB 1; Dako, Glostrup, Denmark) were used in the procedure. Polyclonal Cox-2 antibody (dilution, 1:200; Abcam, Cambridge, MA, USA) was used.

The slides were washed in PBS three times for 3 min each and incubated at 37˚C for 30 min with Advance™ HRP Link (no. K4068; Dako). The slides were then washed with PBS buffer three times for 3 min each and incubated with Advance™ HRP-enzyme at 37˚C for 30 min. The slides were washed in PBS three times for 3 min each and incubated in substrate solution containing 100 mg of 3,3'-diaminobenzidine tetrahydrochloride (no. D-5637; Sigma-Aldrich), 1 ml dimethylsulfoxide, 1 ml H_2O_2 6% (20 volumes) and 100 ml PBS at 37˚C for 5 min under protection from light. The slides were washed in distilled tap water for 3 min. Counterstaining was performed with Harris' hematoxylin for 1 min and the slides were rinsed in distilled tap water. The slides were immersed twice in ammonia (0.5% ammonium hydroxide in water) and then rinsed in distilled tap water. The slides were dehydrated in 80% ethanol for 30 sec, 95% ethanol for 30 sec, 100% ethanol twice for 30 sec each and xylene four times for 30 sec each. The slides were mounted with Entellan Neu (no. 1.07961; Merck, Darmstadt, Germany). The final reaction product observed by microscopy was a golden brown precipitate, which varied depending on the marker.

TMA reading was performed manually by a single experienced pathologist using conventional optical microscopy. The expression of ER and PR, apoptotic (Bcl-2), Cox-2 (Fig. 1) and a proliferation marker (Ki67) were evaluated in the stromal and glandular epithelial tissue. Receptor expression was evaluated by a semi-quantitative method of nuclear reaction for ER, PR and Ki67 and a cytoplasmic reaction for Cox-2 and Bcl-2, analyzing the percentage of stained cells, nuclear staining intensity and final score (19).

The percentage of stained cells was estimated visually. The classification was as follows: Grade 0, no cells stained; grade 1, <1%; grade 2, 1-10%; grade 3, 11-33%; grade 4, 34-66% and grade 5, >66% of cells stained. The staining intensity was also assessed and graded according to the following scale: Grade 0, negative; grade 1, weak; grade 2, moderate; grade 3, severe reaction (19). The sum of positivity and intensity resulted in the final score, ranging from 0-8 (excluding value 1). Ki67 expression was evaluated by immunohistochemistry on a scale from 0 to 3+ and categorized as follows: 0, <10%; 1+, 11-50%; 2+, 51-80%; 3+, >80% of cells showing positivity. The samples containing >10% Ki67 positive cell nuclei were scored as Ki67-positive, those with ≤10% were Ki67-negative (20,21). Appropriate positive and negative controls were used.

Statistical analysis. Clinical characteristics were compared using the χ^2 test, Fisher's exact test or the nonparametric

Mann-Whitney test. For comparison of the median ER, PR, Bcl-2, Cox-2 and Ki67 in the glandular and stromal components, the nonparametric Mann-Whitney test was used. Data were analyzed separately for postmenopausal and premenopausal females. The Statistical Analysis System, version 9.2 (SAS Institute Inc., Cary, NC, USA), was used for calculations. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Overview. Polyps removed from 515 females were analyzed, including 258 from obese (BMI ≥30) and 257 from non-obese (BMI <30) females. The mean age of non-obese females was 53.8 yrs, while obese females was 58.7 yrs on average ($P<0.0001$). Postmenopausal females were also more prevalent in the obese group. The history of hormonal replacement therapy prior to and following menopausal bleeding did not differ between the two groups of obese and non-obese females. Obese females had a higher incidence of hypertension and diabetes mellitus (DM; Table I).

Estrogen and progesterone receptors. A high median PR final score in the stromal and glandular compartments of obese postmenopausal females was identified (median glandular PR: 8 in obese and 7 in non-obese females; $P=0.0057$; median stromal PR: 6 in obese and 5 in non-obese females; $P<0.0001$). However, no differences in ER expression were identified between obese and non-obese females (median glandular ER: 7 in obese and non-obese females; $P=0.139$; median stromal ER: 7 in obese and 6 in non-obese females; $P=0.328$). Among premenopausal females, no difference in ER and PR expression was identified between the obese and non-obese groups. The median rate of ER and PR expression in the premenopausal and postmenopausal females was 7 (Table II).

Cox-2 and Bcl-2. Among postmenopausal females, obese females demonstrated increased Cox-2 and Bcl-2 expression levels in the glandular epithelium compared with non-obese females (median Cox-2 expression in the glandular compartment was 6 in obese and 5 in non-obese females; $P=0.0187$; glandular Bcl-2 was 5 in obese and 3 in non-obese females; $P<0.0001$). Among premenopausal females, obese females demonstrated only an increase in Bcl-2 expression in the glandular epithelium (median expression was 4 in obese and 0 in non-obese females; $P=0.010$). Cox-2 or Bcl-2 expression was null in the stromal compartment in premenopausal or postmenopausal, obese or non-obese females. No other differences were identified in relation to the endometrial stroma (Table III).

Ki67. Regarding Ki67 expression, no statistically significant differences were identified among obese and non-obese postmenopausal females (positive glandular expression was 26% in the obese group vs. 17% in the non-obese group; $P=0.057$; positive stromal expression was 2.5% in the obese group vs. 2.7% in the non-obese group; $P=1.0$) or premenopausal females (positive glandular expression was 26% in the obese group vs. 39% in the non-obese group; $P=0.09$; positive stromal expression was 13% in the obese group vs. 16% in the non-obese group; $P=0.52$; data not shown).

Obesity as a major factor. Analysis of the effects of diabetes and hypertension on study results revealed that alterations in the immunoexpression of the markers were only due to obesity and were not associated with the presence of these comorbid conditions (data not shown).

Discussion

The pathogenesis of endometrial polyps remains poorly understood and few studies have investigated their association with obesity. The present study was conducted to evaluate the effect of obesity on the expression of hormone receptors, Ki67, Bcl-2 and Cox-2 in benign endometrial polyps. Obesity was demonstrated to be associated with PR and Cox-2/Bcl-2 expression in the glandular endometrial compartments of postmenopausal females. In premenopausal females, obesity was associated with Bcl-2 expression in the glandular compartment.

Obesity, which is characterized by increased peripheral aromatization of androgens to estrogens in adipose tissue, appears to be associated with estrogen-induced endometrial abnormalities. Obesity may be important in the pathogenesis of endometrial polyps (9). To the best of our knowledge, no studies on hormonal receptors in endometrial polyps in obese females have been reported to date. This appears to be a highly complex association. In the present study, the high ER expression levels detected in polyps were similar to those observed in previous studies (11,22). However, in the present study, when the expression of the ER was compared, there were no differences in the results between obese and non-obese, premenopausal and postmenopausal females.

This finding is in agreement with a study by Belisário *et al* (11) based on 35 cases of polyps and atrophic endometrial tissue samples from postmenopausal females. The authors also failed to find any association between the BMI and ER expression in polyps. In atrophic endometrial glands, there was an inverse association between BMI and ER expression. No difference was identified between ER and PR expression in endometrial polyps in obese and non-obese females (11). The authors suggested that increased serum estrogen levels observed in obese females were able to reduce ER expression in the atrophic endometrium; however, not in endometrial polyps (11).

The present study demonstrated an increase in PR expression levels in endometrial polyps, in the stromal and glandular tissues of obese postmenopausal females. A study by Gul *et al* (23) reported an increase in PR expression in the stromal compartment associated with increased plasma estrogen levels. This reflected the greater effect of estrogen levels in obese females, since estrogens stimulate the formation of the PR. By contrast, when PR expression and its association with the BMI was directly interrogated, no differences between obese and non-obese females were observed. These results were similar to those obtained by other studies (11,23).

In the present study, Ki67 expression was low and did not show any difference between obese and non-obese females. In 2010, Villavicencio *et al* (24) studied the presence of this marker in normal endometrial tissue and in endometrial cancer. The study showed that Ki67 expression in the endometrium was 9.9-fold higher in overweight females and 12-fold higher in obese females, in comparison with females

Table I. Clinical characteristics of obese and non-obese females undergoing hysteroscopic polypectomy (n=515).

	Obesity status				
	BMI ≥30		BMI <30		
Clinical characteristic	n	%	n	%	P-value[a]
Menopausal status (n=515)					<0.0001
Menopause	204	79.10	150	58.40	
Premenopause	54	20.90	107	41.60	
HRT (n=511)					0.294
Past users	15	5.90	21	8.20	
Never used	241	94.10	234	91.80	
Postmenopausal bleeding (n=354)[b]					0.108
Yes	88	44.2	52	35.6	
No	111	55.8	94	64.4	
Hypertension (n=514)					<0.0001
Yes	191	74.00	107	41.80	
No	67	26.00	149	58.20	
Diabetes mellitus (n=513)					0.0002
Yes	71	27.60	36	14.10	
No	186	72.40	220	85.90	

[a]χ^2 or Mann-Whitney test. [b]In nine cases, patient medical records contained no information. HRT, hormone replacement therapy; BMI, body mass index.

Table II. Median final score of ER and PR in the glandular and stromal compartment of endometrial polyps in postmenopausal and premenopausal females in obese and non-obese groups.

	Obesity status								
	BMI ≥30				BMI <30				
Final score	N[a]	Median	Standard deviation	Median	N[a]	Median	Standard deviation	Median	P-value
Postmenopausal									
Glandular ER	199	6.1	2.6	7.0	147	5.7	2.8	7.0	0.1394
Stromal ER	199	5.6	2.7	7.0	150	5.2	2.9	6.0	0.3286
Glandular PR	**201**	**7.0**	**1.7**	**8.0**	**143**	**6.3**	**2.5**	**7.0**	**0.0057**
Stromal PR	**201**	**5.7**	**2.0**	**6.0**	**146**	**4.8**	**2.3**	**5.0**	**<0.0001**
Premenopausal									
Glandular ER	53	6.0	2.6	7.0	107	6.3	2.4	7.0	0.9970
Stromal ER	54	5.6	2.6	7.0	107	5.7	2.4	7.0	0.9694
Glandular PR	53	6.3	2.2	7.0	106	6.1	2.6	7.0	0.9620
Stromal PR	54	6.6	1.3	7.0	107	6.6	1.8	7.0	0.4095

[a]'N' is variable as the reading of immunohistochemical reactions was compromised by sample attachment in TMA construction in a few cases. [b]Mann-Whitney test. Bold numbers indicate statistical significance. TMA, tissue microarray; BMI, body mass index; PR, progesterone receptor; ER, estrogen receptor; Cox-2, cyclooxygenase-2.

with a normal BMI (24). In the present study, a higher Ki67 concentration in polyps from obese females was expected, and this would have explained why obese females are more likely to develop endometrial pathology, including endometrial polyps. However, a low Ki67 expression was observed in endometrial polyps, with no differences in expression between obese and non-obese females in the present study. To the best of our knowledge, there are no other studies

Table III. Median final score of Cox-2 and Bcl-2 in the glandular and stromal compartments of endometrial polyps in postmenopausal and premenopausal females in obese and non-obese groups.

	Obesity status								
	BMI ≥30				BMI <30				
Final score	N[a]	Median	Standard deviation	Median	N[a]	Median	Standard deviation	Median	P-value
Postmenopausal									
Glandular Cox-2	**201**	**5.4**	**2.2**	**6.0**	**145**	**5.0**	**2.3**	**5.0**	**0.0187**
Stromal Cox-2	201	1.2	2.1	0.0	146	1.1	2.0	0.0	0.5886
Glandular Bcl-2	**201**	**4.2**	**2.5**	**5.0**	**142**	**3.0**	**2.5**	**3.0**	**<0.0001**
Stromal Bcl-2	201	1.0	1.9	0.0	144	1.4	2.2	0.0	0.1975
Premenopausal									
Glandular Cox-2	54	5.5	1.9	6.0	105	6.0	1.7	6.0	0.0807
Stromal Cox-2	54	1.8	2.5	0.0	105	2.3	2.8	0.0	0.2379
Glandular Bcl-2	**53**	**3.3**	**2.4**	**4.0**	**103**	**2.2**	**2.5**	**0.0**	**0.0104**
Stromal Bcl-2	53	1.8	2.4	0.0	103	1.4	2.1	0.0	0.2594

[a]'N' is variable as the reading of immunohistochemical reactions was compromised by sample attachment in TMA construction in a few cases. [b]Mann-Whitney test. Bold numbers indicate statistical significance. TMA, tissue microarray; Cox-2, cyclooxygenase-2; BMI, body mass index; Bcl-2, B-cell lymphoma 2.

directly assessing the presence of Ki67 in endometrial polyps and its correlation with the BMI.

In postmenopausal females, Bcl-2 expression levels in endometrial polyps are increased compared with those in adjacent atrophic endometrial tissue, suggesting that the inhibition of apoptosis is an important mechanism in polyp development (25). Higher Bcl-2 expression levels were observed in the glandular epithelium of polyps from premenopausal and postmenopausal obese females. No differences in the stromal tissue were identified within this group. These results are in agreement with those reported by other studies in which polyps demonstrated low Ki67 expression levels and increased Bcl-2 expression levels (26,27). This corroborates the hypothesis that polyp development is more closely associated with decreased apoptosis than with increased cell division (26,27).

Other studies have also demonstrated an increase in Bcl-2 expression in the glandular epithelium of endometrial lesions, particularly in hyperplasia and endometrial cancer (28). Bcl-2 expression in endometrial glands is likely to have an important role in the early stages of endometrial carcinogenesis (28). It may also be associated with obesity, which is considered a risk factor for endometrial cancer.

The present study evaluated polyps in premenopausal and postmenopausal females. PR expression was highest in the glandular and stromal compartments. The expression of Cox-2/Bcl-2 was highest in the glandular compartments of polyps from obese postmenopausal females. Hormone receptor expression did not differ between premenopausal obese and non-obese females, with the exception of Bcl-2 expression in glandular tissue. Furthermore, McGurgan *et al* (26) compared endometrial polyps in premenopausal and postmenopausal females, reporting that ER expression in the stromal tissue and PR expression in glandular tissue were higher in postmenopausal females. In addition, Ki67 expression was higher in the stromal compartment of premenopausal females. Bcl-2 expression did not differ between premenopausal and postmenopausal females. The authors observed that these findings further strengthen the hypothesis that endometrial polyps do not develop due to increased cell proliferation, but as a result of decreased cell death through apoptosis. However, the exact mechanism of polyp formation remains unknown (26). Gul *et al* reported an increase in PR expression in the stromal compartment of polyps from premenopausal patients, however, ER did not differ statistically (25). The results were discordant from those obtained in the present study, where polyps from postmenopausal females demonstrated the highest expression.

By comparing the levels of Cox-2 in polyps of premenopausal and postmenopausal females, Erdemoglu *et al* (29) discovered an increase in Cox-2 expression in the stromal compartments of polyps from premenopausal females with no difference in the glandular compartments of the polyps (29). This finding is conflicts with the results of the present study, which demonstrated an increase in Cox-2 expression in the glandular epithelium of postmenopausal polyps.

Similarly to other studies, a high Cox-2 expression was observed in endometrial polyps (29). The present study revealed a higher Cox-2 expression in the glandular compartments of polyps from postmenopausal obese females compared with those from non-obese females. This difference was not identified in the stromal compartments or tissue samples from premenopausal females. One possible explanation for these results is an increase in leptin, a hormone secreted by adipocytes. It increases the production and activity of Cox-2, resulting in increased cell proliferation and angiogenesis (17). To the best of our knowledge, there are no studies specifically assessing Cox-2 expression in polyps and its association with obesity. However, the association

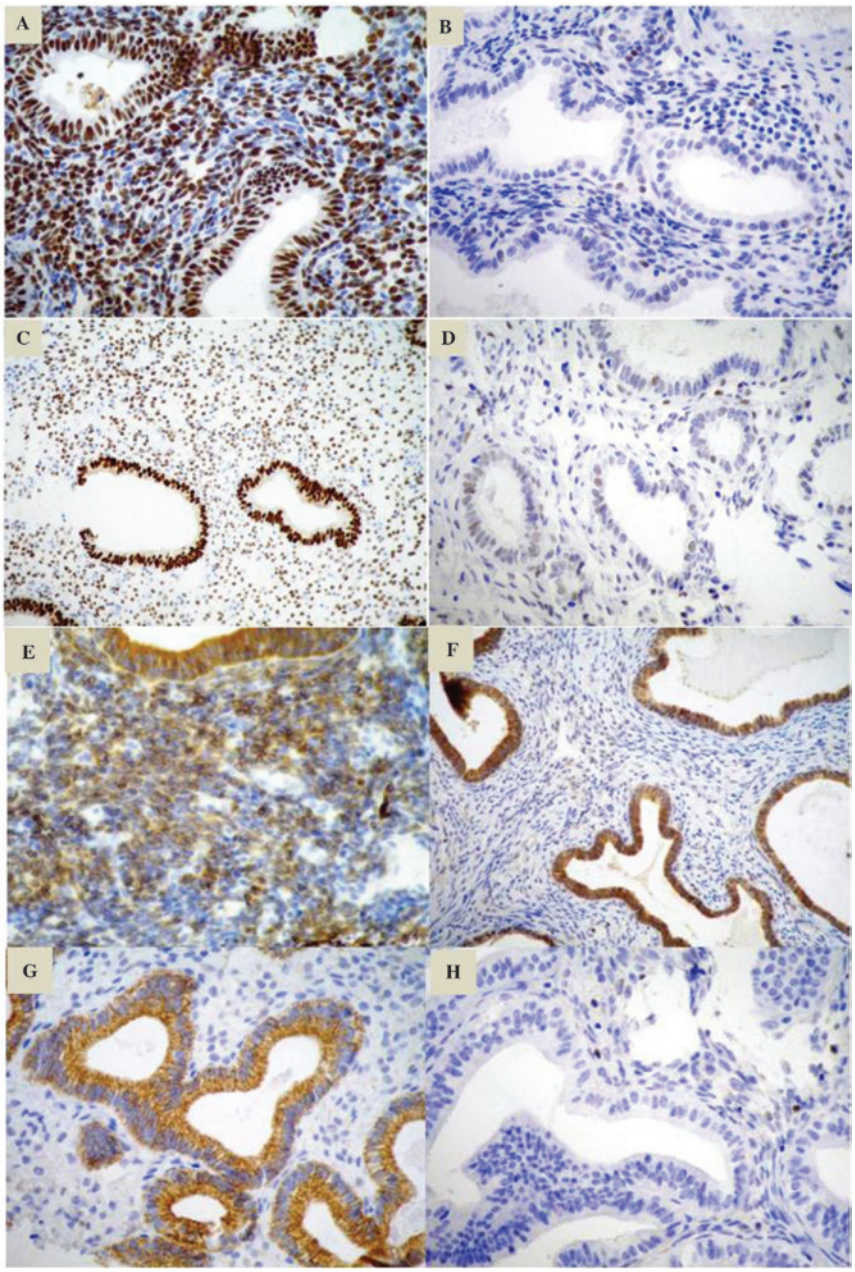

Figure 1. Immunoexpression of receptors in endometrial polyps. (A) Positive ER immunostaining in glandular and stromal compartments (magnification, x40). (B) Negative ER immunostaining in glandular epithelium (magnification, x40). (C) Positive PR immunostaining in glandular epithelium (magnification, x40). (D) Negative PR immunostaining in glandular epithelium (magnification, x40). (E) Positive Cox-2 in glandular epithelium and stroma (magnification, x40). (F) Positive Cox-2 staining in glandular epithelium. (G) Positive Bcl-2staining in glandular epithelium. (H) Negative Bcl-2 staining in glandular epithelium. PR, progesterone receptor; ER, estrogen receptor; Cox-2, cyclooxygenase-2; Bcl-2, B-cell lymphoma 2.

between increased leptin, obesity and increased endometrial Cox-2 expression has been confirmed in studies on females with endometrial cancer (17). Adipose tissue is now considered an active endocrine organ, producing several humoral factors that promote the release of proinflammatory cytokines (adipokines). In obesity, these cytokines contribute to the systemic inflammatory process observed in metabolic syndrome (30).

Clinical evaluation of the patients revealed that hypertension and diabetes were more prevalent in obese females, suggesting that inflammatory factors may have an effect on these patients. This may potentially explain the higher Cox-2 expression in polyps of obese postmenopausal females found in the present study.

Studies have evaluated the presence of inflammatory markers, including C-reactive protein, TNF-α and interleukin-6 in patients with obesity and an increased risk of developing endometrial pathology, including endometrial cancer. Weight loss was demonstrated to reduce the level of these inflammatory markers and the risk of cancer. Furthermore, the presence of markers was important in the development of cancer (31).

To the best of our knowledge, no other studies considered the role of obesity concomitant with the parameters the present study investigated in benign endometrial polyps. Differences between the results of several immunohistochemical studies of endometrial polyps may be explained by differences in popu-

lations evaluated (7,13,11,27). The present study was unique in that it explicitly investigated polyps in obese and non-obese females. Furthermore, most earlier studies were based on a small sample, while the present study covered a significantly larger number of cases. The semi-quantitative nature of the present study contributed to the different results obtained between studies, which were dependent on the criteria used.

In conclusion, the present study suggested that the pathogenesis of endometrial polyps in obese females was able to explain the differences in certain aspects of polyp development in general, including a greater effect of hormone receptors (mainly PRs), inhibition of apoptosis (evidenced by Bcl-2), and inflammation (associated with pro-inflammatory effect of obesity; COX-2), but is poorly correlated with a proliferation marker (Ki67).

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