CARLOS EDUARDO DE GODOY JUNIOR

PREVALÊNCIA DE PÓLIPOS ENDOMETRIAIS PRÉ-MALIGNOS E MALIGNOS EM MULHERES NA PRÉ E NA PÓS-MENOPAUSA E FATORES CLÍNICOS, ULTRASSONOGRÁFICOS E HISTEROSCÓPICOS ASSOCIADOS À MALIGNIDADE

Dissertação de Mestrado

ORIENTADOR: Profª.Drª. LÚCIA HELENA SIMÕES DA COSTA PAIVA

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Dissertação de Mestrado apresentada à Pós-Graduação da Faculdade de Ciências Médicas da Universidade Estadual de Campinas para obtenção do Título de Mestre em Ciências da Saúde, área de concentração Fisiopatologia Ginecológica.

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Dedico este trabalho...

...à minha esposa Carolina,
por dominar a arte de tornar suaves os momentos difíceis,
pela doçura com que divide comigo a vida cotidiana,
e por me dar paz no coração para sonhar e continuar lutando.

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Sumário

Símbolos, Siglas e Abreviaturas

CAISM – Centro de Atenção Integral à Saúde da Mulher

DM – Diabetes Mellitus

FCM – Faculdade de Ciências Médicas

HAS – Hipertensão Arterial Sistêmica

IC – Intervalo de Confiança

IGF – *Insulin-Like Growth Factor*

IMC – Índice de Massa Corporal

QUADAS – *Quality Assessment of Diagnostic Accuracy Studies*

ROC – *Receiver Operating Characteristic*

RP – Razão de Prevalência

TH – Terapia Hormonal

UNICAMP – Universidade Estadual de Campinas

VPN – Valor Preditivo Negativo

VPP – Valor Preditivo Positivo

Resumo

Introdução: Os pólipos endometriais são achados freqüentes em mulheres durante a investigação de sangramento uterino anormal ou sangramento pós-menopausa. Apesar da baixa malignidade associada aos pólipos, a ressecção histeroscópica das lesões é conduta de rotina, levando diversas pacientes portadoras de lesões benignas à realização de tratamentos cirúrgicos. A partir disso, surge a necessidade de identificar fatores de risco para malignidade e métodos propedêuticos que tornem a indicação cirúrgica mais criteriosa. **Objetivos:** Avaliar a prevalência de pólipos endometriais pré-malignos e malignos em mulheres na pré e na pós-menopausa e fatores clínicos, ultrassonográficos e histeroscópicos associados à malignidade. **Sujeitos e Métodos:** Foram selecionadas mulheres submetidas a ressecção histeroscópica de pólipos endometriais de janeiro de 1998 a dezembro de 2008, utilizando-se a base de dados informatizada do Hospital da Mulher Prof. Dr. José Aristodemo Pinotti - CAISM/UNICAMP. Foram incluídas 870 mulheres, com idades entre 25 e 85 anos, agrupadas em pré-menopausa ou pós-menopausa. Os dados clínicos, ultrassonográficos, histeroscópicos e histológicos foram obtidos através da revisão dos prontuários médicos. As variáveis clínicas avaliadas foram idade, sangramento pós-menopausa, tempo de menopausa, paridade, hipertensão arterial, obesidade,

diabetes mellitus, uso de terapia hormonal e uso de tamoxifeno. Os pólipos foram classificados em benignos (pólipos endometriais, pólipos com hiperplasia simples ou complexa sem atipias), pré-malignos (pólipos com hiperplasia simples ou complexa com atipias) e pólipos malignos. **Resultados:** A média etária foi de 57,5 anos ($\pm$ 10,6), sendo que 76,4% encontravam-se na pós-menopausa. Foram diagnosticadas 95,8% de lesões benignas. Pólipos pré-malignos foram 1,6% dos casos. Pólipos malignos representaram 2,5% do total da amostra. O sangramento pós-menopausa e a idade avançada foram os únicos fatores clínicos associados ao maior risco de malignidade com RP de 3,67 (IC95% 1,69 - 7,97) e RP de 1,05 (IC95% 1,01 – 1,09), respectivamente. A avaliação ultrassonográfica da linha endometrial revelou maior espessura média nos pólipos malignos. Na histeroscopia cirúrgica, os maiores pólipos ressecados foram aqueles com hiperplasia complexa sem atipias, seguidos pelos pólipos carcinomatosos e pólipos com hiperplasia complexa com atipias. A medida ultrassonográfica da espessura endometrial de 13mm mostrou uma acurácia de 68,6% para o diagnóstico de malignidade, com sensibilidade de 69.6%, especificidade de 68,5%, VPP de 9,3% e VPN de 98%. Os pólipos de 30mm medidos pela histeroscopia mostraram uma acurácia de 65,3% para o diagnóstico de malignidade com sensibilidade de 47,8%, especificidade de 66,1%, VPP de 6,1% e VPN de 96,5%. **Conclusões:** A prevalência de malignidade nos pólipos endometriais foi baixa e esteve associada ao sangramento pós-menopausa e maior idade. A espessura endometrial à ultrassonografia e o tamanho dos pólipos endometrias à histeroscopia tiveram baixa acurácia para predizer malignidade nos pólipos endometriais.

Summary

Introduction: Endometrial polyps are frequent findings in women during investigation of abnormal uterine bleeding or postmenopausal bleeding. Despite the low malignancy rate associated with polyps, hysteroscopic resection of the lesions is routine practice, leading to surgical treatment in various patients with benign lesions. Therefore, there is a need to identify risk factors for malignancy and propaedeutic methods that can permit a more judicious indication for surgery. **Objectives:** To evaluate the prevalence of premalignant and malignant endometrial polyps in premenopausal and postmenopausal women, as well as clinical, ultrasound and hysteroscopic factors associated with malignancy. **Subjects and Methods:** Women undergoing hysteroscopic resection of endometrial polyps from January 1998 to December 2008 were selected, using a computerized database from the Prof. Dr. José Aristodemo Pinotti Women's Hospital- CAISM/UNICAMP. Eight hundred and seventy (870) women, aged between 25 and 85 years, grouped into premenopausal or postmenopausal were included in the study. Clinical, ultrasound, hysteroscopic and histologic data were obtained by medical chart review. The clinical variables evaluated were age, postmenopausal bleeding, time since menopause, parity, arterial hypertension, obesity, diabetes mellitus,

hormonal therapy use and tamoxifen use. Polyps were classified as benign (endometrial polyps, polyps with non-atypical simple or complex hyperplasia), premalignant (polyps with atypical simple or complex hyperplasia) and malignant polyps. **Results:** The mean age of the patients was 57.5 years (± 10.6), and 76.4% of these women were postmenopausal. Benign lesions were diagnosed in 95.8% of the patients. Premalignant polyps represented 1.6% of the cases. Malignant polyps accounted for 2.5% of the total sample. Postmenopausal bleeding and advanced age were the only clinical factors associated with a higher risk of malignancy with RP of 3.67 (95%CI 1.69 – 7.97) and RP of 1.05 (95%CI 1.01 – 1.09), respectively. Ultrasound evaluation of the endometrial thickness revealed that malignant polyps had a greater median thickness. On surgical hysteroscopy, the largest resected polyps were those with complex non-atypical hyperplasia, followed by carcinomatous polyps and polyps with atypical complex hyperplasia. A sonographically measured endometrial thickness of 13mm showed a diagnostic accuracy of 68.6% for malignancy, with a sensitivity of 69.6%, a specificity of 68.5%, PPV of 9.3% and NPV of 98%. Polyps of 30mm measured by hysteroscopy showed a diagnostic accuracy of 65.3% for malignancy with a sensitivity of 47.8%, a specificity of 66.1%, a VPP of 6.1% and a VPN of 96.5%. **Conclusions:** There was a low prevalence of malignancy in endometrial polyps that was associated with postmenopausal bleeding and more advanced age. Endometrial thickening on ultrasound evaluation and endometrial polyp size on hysteroscopy is able to predict malignancy in endometrial polyps with a low level of accuracy.

1. Introdução

Segundo relatório da Agência Internacional para Pesquisa em Câncer, da Organização Mundial da Saúde, estima-se que no ano de 2008, cerca de 12 milhões de casos novos de câncer foram diagnosticados e 7 milhões de pessoas morreram em decorrência da doença. Devido ao crescimento populacional e ao aumento no número de idosos, a incidência de neoplasias malignas apresenta índices crescentes, com maior impacto recaindo sobre os países em desenvolvimento (1).

Diante desse cenário, diversos investimentos vêm sendo feitos no desenvolvimento de ações abrangentes para o controle do câncer, no sentido de promoção de saúde, detecção precoce, assistência aos pacientes, formação de recursos humanos, comunicação social e pesquisa científica.

Nos países desenvolvidos, o câncer de endométrio apresenta-se como a quarta maior incidência em mulheres, com 43.720 casos novos diagnosticados em 2010, com cerca de 7950 mortes atribuídas à doença (2). No Brasil, a incidência mediana de câncer de endométrio é de 6 casos novos para cada cem mil mulheres, a cada ano (3).

O carcinoma de endométrio é mais freqüente em pacientes na pós-menopausa, com pico de incidência ao redor dos 60 anos de idade. O sangramento uterino na pós-menopausa constitui o principal sintoma associado ao diagnóstico de neoplasia maligna endometrial, estando presente em até 90% dos casos (4).

A evolução do conhecimento acerca da fisiopatologia do câncer de endométrio, aliado aos avanços tecnológicos empregados na medicina diagnóstica nos últimos anos, permitem identificar quais as pacientes sob maior risco. A partir disso, surge a necessidade de estabelecer estratégias para diagnosticar a existência de lesões precursoras ou casos de câncer de endométrio em estágio inicial, permitindo tratamento precoce e melhora nos índices de sobrevida.

Entretanto, a falta de métodos de rastreamento adequados e a impossibilidade de excluir a presença de malignidade sem a realização de exame histológico de amostra endometrial, contribui em muitos casos para a realização de procedimentos cirúrgicos excessivos, submetendo diversas pacientes portadoras de lesões benignas intra-uterinas a procedimentos de anestesia e biópsia sem indicação precisa, resultando em maior exposição de pacientes a riscos anestésicos e cirúrgicos e maior dispêndio pelo sistema de saúde.

A ultrassonografia transvaginal é o principal exame utilizado para avaliação de pacientes com sintomas de sangramento uterino anormal ou sangramento uterino no período pós-menopausa. Em meta-análise realizada por Smith-Bindman et al, com 6000 mulheres submetidas a ultrassonografia por sangramento pós-menopausa e considerando-se anormal a espessura endometrial superior a

5mm, obteve-se sensibilidade de 95% para diagnóstico de doença endometrial em mulheres sem uso de terapia hormonal (TH) e 91% para mulheres que utilizavam TH (5).

Com o crescente uso da ultrassonografia convencional, histerossonografia ou histeroscopia para o diagnóstico de doenças uterinas, o achado de pólipos endometriais tornou-se mais freqüente nos últimos vinte anos. Os pólipos endometriais são diagnosticados em 10 a 40% das mulheres com sangramento uterino anormal (6-10) e em 1 a 12% das mulheres assintomáticas durante exame ultrassonográfico de rotina (11,12).

Os pólipos endometriais são definidos como o crescimento de tecido endometrial localizado, de forma pediculada ou séssil, podendo ser únicos ou múltiplos, de poucos milímetros a vários centímetros de tamanho, contendo quantidades variáveis de estroma e vasos sangüíneos, recobertos por epitélio pseudo-estratificado (13).

Apesar dos pólipos endometriais serem achados freqüentes, sua etiogenia e patogênese permanecem incertas. O estímulo para o surgimento dos pólipos ainda é desconhecido, porém acredita-se que exista intensa influência hormonal (14). Diversas pesquisas demonstram expressão aumentada de receptores de estrógeno e progesterona nos pólipos, quando comparada ao endométrio adjacente, sugerindo que os receptores esteróides possuem papel crucial na fisiopatologia dos pólipos endometriais, tornando-os mais sensíveis à concentração local destes hormônios (15).

A expressão de receptores de estrógeno e progesterona nos pólipos endometriais difere na pré e na pós-menopausa. Estudo desenvolvido por Taylor et al, demonstrou que durante a fase secretória do ciclo menstrual, ocorre aumento na expressão de receptores de estrógeno e progestrona no epitélio glandular dos pólipos endometriais. Esse comportamento difere daquele apresentado pelo endométrio adjacente, em que os receptores de estrógeno apresentam redução em sua expressão durante a fase secretória, em resposta ao aumento na concentração local de progestrona (16).

Na pós-menopausa, ocorre significativo aumento na expressão de receptores de estrógeno e progesterona, quando comparado aos pólipos na pré-menopausa. Este aumento pode representar um mecanismo adaptativo dos pólipos endometriais frente à reduzida concentração de hormônios esteróides locais (14).

Sabe-se que em mulheres na pós-menopausa que fazem uso de terapia hormonal, existe maior risco para o surgimento de pólipos endometriais ou proliferação de pólipos já existentes. O uso de TH parece não alterar a expressão de receptores de estrógeno e progesterona nos pólipos endometriais, devido a baixa oferta exógena destes hormônios. Entretanto, o uso de TH aparentemente promove inibição de apoptose em pólipos endometriais, o que afeta diretamente seu processo de crescimento (17-19). Mulheres que apresentam pólipos endometriais não possuem risco aumentado para surgimento de lesões pré-malignas ou malignas durante o uso de TH (20). Além disso, o uso de TH com associação de estrógeno e progesterona não representa fator de risco para o desenvolvimento

de câncer de endométrio, quando comparado a pacientes que não utilizam terapia hormonal (21-23).

Além das alterações na expressão de receptores, os pólipos endometriais parecem apresentar também expressão aumentada de Bcl-2, marcador celular envolvido com mecanismos de inibição de apoptose, além de redução na expressão de Ki67, cuja expressão se relaciona com processos de proliferação celular. Essas características sugerem que sua origem provável se deve à falha nos mecanismos de morte celular programada e não propriamente devido à proliferação celular desordenada (24,25).

Apesar de geralmente os pólipos serem considerados benignos, a prevalência de carcinoma associado aos pólipos endometriais varia de 0,8% a 8%, dependendo da seleção de pacientes e dos métodos utilizados no diagnóstico e ressecção (6,26).

São fatores de risco estabelecidos para malignidade endometrial, a idade avançada, obesidade, ciclos menstruais anovulatórios, menopausa tardia, nuliparidade, diabetes mellitus, hipertensão arterial, uso de tamoxifeno e síndromes hereditárias que elevam a prevalência de neoplasia de cólon e endométrio - Lynch II (17).

A literatura demonstra que o risco de surgimento de pólipos endometriais pré-malignos ou malignos pode ser até cinco vezes maior em mulheres com idade superior a 60 anos (4,27,28).

Mulheres submetidas à exposição prolongada do endométrio à ação estrogênica, sobretudo quando não há efeito opositor da progesterona, apresentam maior risco para surgimento de pólipos endometriais e câncer de endométrio (29). A associação de idade avançada, hipertensão arterial e obesidade aparentemente contribuem para a patogênese dos pólipos endometriais (19,30).

Outro fator descrito por Rahimi et al, diz respeito ao tamanho dos pólipos endometriais, que apresentam relação direta com a existência de hiperplasia atípica e carcinoma de endométrio. Em mulheres na pós-menopausa, pólipos maiores que 1,5cm possuem 3,6 vezes maior risco de malignidade do que lesões de pequeno diâmetro (31).

Dentre os tipos histológicos, os carcinomas endometrióides são mais comumente diagnosticados na superfície de pólipos endometriais. Além disso, alguns tipos histológicos, como os carcinomas serosos, apesar de menos prevalentes, tendem a surgir na superfície de pólipos endometriais e estão associados a pior prognóstico (28,32,33).

No processo de carcinogênese endometrial, observa-se aumento na biossíntese intratumoral de estrogênio, em mecanismo dependente da ação de aromatase e prostaglandinas. A expressão acentuada de aromatase na existência de malignidade sugere maior produção local de estrogênio, em oposição com a baixa atividade desta enzima nos tecidos desprovidos de doença (34). As Prostaglandinas, por sua vez, induzem aumento na expressão e atividade de

aromatase. Esta relação direta representa importante mecanismo parácrino e autócrino de elevação da concentração estrogênica intratumoral (35).

O uso de tamoxifeno no tratamento de mulheres com câncer de mama promove aumento no risco de surgimento de pólipos endometriais, hiperplasia endometrial e câncer de endométrio. Isso decorre da ação antagonista do tamoxifeno em receptores estrogênicos mamários e ação agonista em receptores estrogênicos endometriais. Sabe-se que o uso do medicamento por período superior a 5 anos está associado a maior incidência de neoplasia maligna endometrial e piora nos índices de sobrevida em comparação com pacientes que não utilizam o medicamento (36-38). Em pacientes usuárias de tamoxifeno, o risco de malignidade dos pólipos endometriais também está aumentado, sendo encontrados em 3 a 10,7% dos casos (39-41).

O carcinoma de endométrio originado na superfície de um pólipo endometrial não difere quanto ao prognóstico e evolução quando comparado às neoplasias originadas no endométrio na ausência de pólipos endometriais. Os principais fatores envolvidos com o prognóstico são o estadiamento inicial, o tipo histológico e o grau de diferenciação celular (33).

Entretanto, existem diversas dúvidas a respeito da necessidade de ressecção cirúrgica dos pólipos endometriais, sobretudo em pacientes assintomáticas, na pré-menopausa ou que não preencham critérios de risco para neoplasia maligna endometrial.

Atualmente, a histeroscopia representa o padrão ouro para o diagnóstico de doenças endometriais, com sensibilidade de 90% para lesões atróficas, 95% para pólipos, 92% para hiperplasias típicas, 87% para hiperplasias atípicas e 94% para carcinoma de endométrio (42). Entretanto, o custo envolvido com aquisição e manutenção de instrumental cirúrgico, além da necessidade de treinamento específico do cirurgião ginecológico, fazem com que sua realização ainda fique restrita apenas a determinados centros.

Dentre os métodos utilizados para obtenção de amostra tecidual, a polipectomia histeroscópica é superior em relação à curetagem uterina, pois a primeira permite a retirada completa da lesão, enquanto que a última permite a retirada de fragmentos não representativos, com biópsia inadvertida do endométrio adjacente (43).

Em estudo com 335 mulheres submetidas à histeroscopia por sangramento pós-menopausa, verificou-se que 42% sangravam por atrofia, 48% por doença intracavitária benigna (85% sendo pólipos) e 9,6% por lesões proliferativas (50% hiperplasias e 50% carcinomas) (44).

A conduta expectante frente à polipectomia histeroscópica deve levar em consideração a idade da paciente, os fatores de risco associados à malignidade, os fatores de risco associados aos procedimentos anestésico e cirúrgico e o desejo da paciente em prosseguir a investigação complementar. É de fundamental importância, conhecer os riscos e benefícios de cada método diagnóstico e considerar, em conjunto com a paciente, qual a melhor conduta a

adotar frente ao achado de espessamento endometrial, sangramento uterino anormal ou sangramento pós-menopausa.

O seguimento clínico pode ser considerado aceitável em mulheres assintomáticas na pré-menopausa, em que as chances de malignidade são pequenas. Em mulheres inférteis, sabe-se que a ressecção de pólipos endometriais está associada a melhora nas taxas de fertilidade (45).

Mulheres na pré-menopausa que possuem sangramento intermenstrual associado à presença de pólipos endometriais, apresentam singnificativa melhora nos sintomas quando ressecados os pólipos endometriais. Para pacientes sofrendo de acentuado sangramento uterino na presença de pólipos endometriais, acredita-se que a polipectomia histeroscópica não traz resultados satisfatórios, sendo necessário a ressecção mais ampla do endométrio adjacente ou o uso de dispostivo intra-uterino com levonorgestrel para redução de sangramento (46).

Diante disso, é de fundamental importância determinar quais as pacientes com pólipos endometriais sob maior risco de malignidade e qual a necessidade de ressecção de pólipos endometriais em pacientes na pré e na pós-menopausa visto que a maioria dos pólipos ocorrem em pacientes idosas, muitas vezes com comorbidades que acrescentam maior risco cirúrgico. A partir dos dados obtidos, pretende-se determinar de maneira mais criteriosa, quais as pacientes portadoras de pólipos endometriais que necessitam de tratamento cirúrgico pelo maior risco de malignidade e que deveriam ter prioridade na realização do procedimento.

2. Objetivos

2.1. Objetivo geral

Avaliar a prevalência de pólipos endometriais pré-malignos e malignos em mulheres na pré e na pós-menopausa e fatores clínicos, ultrassonográficos e histeroscópicos associados à malignidade.

2.2. Objetivos específicos

- Determinar a prevalência de pólipos endometriais pré-malignos e malignos em mulheres na pré e na pós-menopausa, submetidas à polipectomia histeroscópica.
- Avaliar características clínicas e fatores associados à malignidade dos pólipos endometriais.
- Avaliar a associação entre as características ultrassonográficas e o diagnóstico histológico dos pólipos endometriais.
- Avaliar a associação entre as características histeroscópicas e o diagnóstico histológico dos pólipos endometriais.

3. Publicações

Artigo 1 - **Risk of malignancy in endometrial polyps in premenopausal and postmenopausal women according to clinicalpathologic characteristics**

Costa-Paiva L; Godoy Jr, CE; Antunes Jr, A; Arthuso M; Pinto-Neto AM

Artigo submetido ao *The Journal of the North American Menopause Society*

Artigo 2 - **Accuracy of sonography and hysteroscopy in the diagnosis of premalignant and malignant polyps in postmenopausal women**

Godoy Jr, CE; Costa-Paiva L; Antunes Jr, A; Morais, SS; Pedro, AO; Pinto-Neto AM

3.1. Artigo 1

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Action	Manuscript Number	Title	Initial Date Submitted	Status Date	Current Status
Action Links		Risk of malignancy in endometrial polyps in premenopausal and postmenopausal women according to clinicalpathologic characteristics	Feb 01, 2011	Feb 01, 2011	Submitted to Journal

Page: 1 of 1 (1 total submissions) Display 10 results per page.

Risk of malignancy in endometrial polyps in premenopausal and postmenopausal women according to clinicalpathologic characteristics

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Summary

Objectives: To evaluate the prevalence of endometrial premalignant and malignant polyps in premenopausal and postmenopausal women as well as clinical, ultrasound and hysteroscopic factors associated with malignancy. **Subjects and Methods:** All women undergoing hysteroscopic resection of endometrial polyps from January 1998 to December 2008 were selected, using computerized database from the operating theater of the Prof. Dr. José Aristodemo Pinotti Women's Hospital – CAISM/UNICAMP. Eight hundred-seventy women ages ranging from 25 to 85 years were included. Polyps were classified into benign (endometrial polyps, polyps with non-atypical simple hyperplasia and non-atypical complex hyperplasia), premalignant (polyps with atypical simple hyperplasia or atypical complex hyperplasia) and malignant polyps. Statistical analysis was performed by measurement of the frequencies, means and standard deviation. The risk factors for malignancy were assessed by bivariate analysis and multiple regression analysis, using the Epi-Info 2000 program and SAS (Statistical Analysis Software) version 9.2. **Results:** The mean age of the patients was 57.5 ($\pm$ 10.6) year. Of these women, 76.4% were postmenopausal. Women were diagnosed with benign lesions in 95.8% of cases. Premalignant polyps accounted for 1.6% of the total number of cases. Malignant polyps represented 2.5% of the total sample. Postmenopausal bleeding and age over 60 years were the only factors that remained associated with a higher risk of malignancy with a RP of 3.67 (95%CI 1.69 – 7.97) and a RP of 1.05 (95%CI 1.01 – 1.09). **Conclusion:** The prevalence rate of malignancy in endometrial polyps was low and was associated with postmenopausal bleeding and advanced age.

Key words: *endometrial polyps, endometrial thickness, hysteroscopy, risk factors, malignancy.*

1. Introduction

With the increased use of ultrasound, hysterosonography and hysteroscopy in the evaluation of patients with abnormal uterine bleeding or postmenopausal bleeding, the diagnosis of endometrial polyps became more frequent in the last few years. The prevalence of endometrial polyps ranges from 10 to 40% (1-5) in women with abnormal uterine bleeding and polyps are found in up to 12% of asymptomatic women in routine examinations (6,7).

Endometrial polyps are defined as overgrowths of localized endometrial tissue. Polyps may be pedunculated or sessile, single or multiple, ranging in size from a few millimeters to many centimeters. These lesions may contain varying amounts of stroma and blood vessels, covered by pseudostratified epithelium (8).

It is well-known that the prevalence of malignancy associated with endometrial polyps ranges from 0.8 to 8%, depending on the sample analyzed and the resection methods used (9-16).

Previous studies have demonstrated a significant increase in the incidence of premalignant and malignant polyps in menopausal women, aged over 60 years and who have associated vaginal bleeding (10, 17) Some studies have also observed an association with other risk factors for malignancy such as obesity, use of tamoxifen, arterial hypertension and diabetes mellitus (18).

Hysteroscopy is considered the gold standard in the resection of endometrial polyps and evaluation of the endometrial cavity, because it allows for the complete removal of the lesion and biopsy of suspicious areas in the adjacent endometrium (11). This method has a sensitivity of 94% and specificity

of 58% for the diagnosis of endometrial polyps, surpassing exclusive ultrasound evaluation, with values of 72% and 50%, respectively (19).

Despite the low prevalence rate of malignancy, various patients have undergone surgical procedures for the removal of polyps without a precise indication. Thus, it is imperative to determine which patients are at greater risk so that a more judicious surgical indication for hysteroscopic resection of endometrial polyps can be made.

The aim of the study was to determine the prevalence of premalignant and malignant endometrial polyps in premenopausal and postmenopausal women. All women evaluated in this study underwent hysteroscopic resection of endometrial polyps and compose one of the largest case studies investigating the topic in the literature. Furthermore, associations between clinical, ultrasound and hysteroscopic factors as well as the risk of malignancy were evaluated.

2. Materials and Methods

This study was conducted in the Prof. Dr. José Aristodemo Pinotti Women's Hospital – CAISM/UNICAMP and was approved by the Research Ethics Committee of the UNICAMP Medical School under number 769/2009.

According to information contained in the computerized database of this institution 6018 surgical hysteroscopies were performed in this service from January 1998 to December 2008, for the diagnosis and treatment of diverse uterine conditions. Of the women examined, 1050 underwent surgical treatment for endometrial polyps (Flow chart annexed).

Eight hundred and seventy (870) women were included in the study, ages ranging from 25 to 85 years. These women were grouped according to menopausal status into premenopausal or postmenopausal. Menopause was considered amenorrhea lasting more than 12 months.

Women included in the study had a previous diagnosis of endometrial polyp by ultrasound or diagnostic hysteroscopy.

Excluded from the sample were patients in whom resection of the lesion was not possible or there was no histologic confirmation of endometrial polyp.

Clinical, pathological anatomy, ultrasound and hysteroscopic data were obtained by reviewing medical charts. A chart elaborated as an instrument for data collection was used. Clinical variables assessed were age, postmenopausal bleeding, time since menopause, parity, arterial hypertension, obesity, diabetes mellitus, use of hormone therapy and use of tamoxifen.

A diagnosis of endometrial polyp by ultrasound was made following a finding of focal endometrial thickening, associated with the presence of vascular pediculum. Diagnostic hysteroscopy was performed by using a 2.8mm optical system (Karl Storz, Germany). For distension of the uterine cavity, CO2 and saline infusion were used. Evaluation of the endocervical canal, endometrial surface, vascularity, tubal ostia, presence of endometrial polyps, myomas or synechiae was performed.

Surgical hysteroscopy was performed by a gynecologist with the patient under spinal anesthesia. A 10-mm resectoscope was used for the surgical procedure (Karl Storz, Germany). Distension of the uterine cavity was obtained by use of 1.5% glycine solution. The endocervical channel and endometrial

cavity were evaluated. Resection of endometrial polyps was performed by electrocautery using monopolar energy.

Pathologists from the Department of Pathological Anatomy of the UNICAMP Medical School analyzed the endometrial samples obtained, using hematoxilin and eosin staining. Polyps were classified as benign, non-atypical simple hyperplasia, non-atypical complex hyperplasia, atypical simple hyperplasia, atypical complex hyperplasia and malignant.

3. Statistical analysis

On bivariate analysis, the relative risk with 95% confidence intervals was calculated. Subsequently, multiple regression analysis was performed in a model with independent variables such as age, time since menopause in years, menopausal status, use of hormone therapy, body mass index (BMI), parity, presence of diabetes mellitus, presence of systemic arterial hypertension, use of tamoxifen, presence of postmenopausal bleeding, endometrial thickening and size of the endometrial polyp in surgical hysteroscopy. The Epi-Info 2000 program and SAS (Statistical Analysis Software) version 9.2 were used for these calculations. The significance level was set at $p<0.05$.

4. Results

The mean age of the women was 57.5 ($\pm$ 10.6) years and 76.4% were postmenopausal. The mean time since menopause was 12.4 ($\pm$ 8.95) years. The diagnosis of arterial hypertension was present in 58.2% of cases, while obesity (BMI higher than or equal to 30 Kg/m^2) was found in 45.8% of the patients.

Vaginal bleeding was reported by 39.6% of postmenopausal women. Among menopausal women, endometrial thickness was greater than 5 mm on ultrasound evaluation in 89.8% of cases and these women received a diagnosis of endometrial thickening. Table 1 shows the clinical characteristics of patients who underwent hysteroscopic resection of endometrial polyps.

Table 2 shows the histologic diagnosis of resected lesions. Eight hundred and thirty-four (834) benign lesions were diagnosed (95.9%), including 671 endometrial polyps (77.1%), 95 polyps with non-atypical simple hyperplasia (10.9%) and 5 polyps with non-atypical complex hyperplasia (0.57%) and 63 other findings such as submucosal myomas, secreting endometrium, proliferative endometrium, atrophic endometrium or insufficient material for diagnosis (7.24%). Premalignant lesions consisted of 8 polyps with atypical simple hyperplasia (0.91%) and 6 polyps with atypical complex hyperplasia (0.68%). Twenty-two (22) malignant polyps (2.5%) were diagnosed.

Table 3 shows the factors associated with the risk of malignancy. Of these factors, only postmenopausal bleeding, arterial hypertension, obesity and polyps larger than 15mm showed any significant association ($p < 0.05$). Women with postmenopausal bleeding had a PR of 3.73 (95%CI 1.75 – 7.97). Obese women showed a PR of 2.0 (95%CI 1.02 – 3.93). The presence of arterial hypertension showed a PR of 2.08 and polyps larger than 15mm had a PR of 2.41 despite having non-significant confidence intervals, showing only a trend towards an increased risk.

On multiple regression analysis, the presence of postmenopausal bleeding and age were the only factors associated with a higher risk of malignancy with a PR

of 3.67 (95%CI 1.69 – 7.97) and PR of 1.05 (95%CI 1.01 – 1.09), respectively (Table 4).

5. Discussion

This study was carried out to evaluate the prevalence of premalignant and malignant endometrial polyps, as well as factors associated with malignancy, in a large case study undergoing polypectomy by hysteroscopy. The results showed that the prevalence of premalignant and malignant polyps was low. Furthermore, it was associated with the presence of postmenopausal bleeding and advancing age. The majority of women were older than 50 years, postmenopausal and had comorbidities.

The prevalence of premalignant and malignant polyps was 4.1%. A previous study conducted by our group with 50% of the case study showed a prevalence of 3.8% (10). These findings are similar to those of other studies showing a prevalence of malignancy in endometrial polyps ranging from 0.8 to 8% (1, 9, 11, 13, 14, 16). These differences in prevalence rates observed may be attributed to different study designs, sample sizes, inclusion and exclusion criteria and different methods used for the diagnosis of polyps, such as transvaginal ultrasound, hysterosonography and hysteroscopy (19).

In a recent meta-analysis published by Lee et al, including 17 studies with a total number of 10.572 premenopausal and postmenopausal women, the prevalence of premalignancy and malignancy was 3.57% (20). In this study, cases of atypical endometrial hyperplasia and endometrial carcinoma were grouped together. These two cases were grouped together because atypical polyps have an elevated rate of malignant transformation (up to 28% of cases). In addition, it is

well-known that endometrial carcinoma is diagnosed in up to 42.6% of women with premalignant endometrial polyps, when hysterectomy is performed (21).

In our case study, the presence of postmenopausal bleeding was the main risk factor for malignancy. Women with postmenopausal bleeding had a 3.73-fold higher risk of developing malignance than asymptomatic women. This association has also been reported in the majority of studies in the literature.

In a meta-analysis, 4.15% of women with abnormal uterine bleeding had endometrial polyps, with a PR of 1.97 (95%CI 1.24 – 3.14). Among asymptomatic women, the prevalence of endometrial polyps was only 2.16%. Considering patients with postmenopausal bleeding and endometrial polyps, the prevalence of malignancy was 4.47%, in comparison to 1.51% among asymptomatic women, with a PR of 3.36 (95%CI 1.45 – 7.80).

Regarding menopausal status, despite a higher prevalence of malignancy in postmenopausal women compared to premenopausal women (4.67% versus 1.95%), we did not observe a significant association (p=0.08) and only noted a statistical trend (PR 2.40 95%CI 0.86 to 6.71). Of the 17 studies included in the meta-analysis, 12 revealed increased risk for malignancy in postmenopausal women, with a PR of 3.86 (2.93 – 5.11) (20).

Age was a risk factor for malignancy in our study. The prevalence of malignant polyps was 3.7% in women younger than 40 years, 3.11% in women aged between 40 and 59 years and 5.36% in women older than 60 years. On multiple regression analysis, the PR for malignancy was 1.05 (95%CI 1.01-1.09). In a research study conducted in this service by Antunes et al with 475 women aged over 60 years, the PR was 4.71 (95%CI 1.08 – 20.56). The distinct

relative risks found among studies with different case studies may be attributed to the larger number of malignant endometrial polyps diagnosed in women aged younger than 60 years in the current study, promoting modifications in the prevalence of malignancy among the age groups considered.

The presence of obesity (BMI> 30 kg/m^2) was also associated with malignancy in endometrial polyps. Obese women have higher concentrations of serum estrogen, leading to a greater stimulation of endometrial proliferation. As a consequence, there is the appearance of benign endometrial polyps, premalignant or malignant lesions (22).

Hypertension has been recognized as a risk factor for hormone-dependent neoplasms in women because it promotes a decrease in the mechanisms of cell apoptosis, favoring tumor growth (23). In the present study, we identified a trend towards a higher risk of malignancy in hypertensive women. In a meta-analysis by Lee et al, only studies by Savelli and Baiocchi reported a significant association between arterial hypertension and the presence of malignant endometrial polyps.

Diabetes mellitus is related to an increased risk of malignant endometrial neoplasms, due to cellular alterations mediated by IGF in states of hyperinsulinemia (24). A correlation between DM and malignant endometrial polyps has been studied by various authors. This association was only present in a study carried out by Gregoriou et al (22). In our study, there was no significant association between these two variables.

Similar to findings observed by other authors, the risk of premalignant or malignant lesions in endometrial polyps was not shown to be influenced by parity, use of HT and use of tamoxifen (10,11,13).

Concerning polyp size, the prevalence rate of malignancy in lesions larger than 15mm was 5.06% compared to 2.09% in polyps of a smaller diameter. No significant association has been observed, only a statistical trend, with PR of 2.41 (95%CI 0.98 to 5.93). Few studies have evaluated the relationship between polyp size and malignancy risk. Some authors have suggested that larger polyps are associated with a higher risk of malignancy (14-16). According to Goldstein (3), Gregoriou (22), Fernandez-Parra (25) and Shushan (26), polyp size does not represent a risk factor for malignancy. In the meta-analysis, polyps are reported by different units of measurement (centimeters, millimeters or grams), making analysis of this association more difficult.

One limitation of this study was data collection. Data was collected exclusively from medical charts that may be responsible for incomplete or inconsistent information. However, it is worth mentioning that this study was conducted with a large sample size using surgical hysteroscopy. This technique permits direct removal of the lesion, reducing the possibility of a misdiagnosis. Furthermore, the prevalence of premalignant and malignant polyps can be more adequately estimated.

6. Conclusion

From the results of this study, we conclude that women with endometrial polyps and postmenopausal bleeding have a higher risk of developing endometrial neoplasm and should undergo hysterocopic resection of the lesions. Due to the low prevalence rate of malignancy in asymptomatic young women with no risk factors, routine removal of the lesions might be avoided because it is not cost-effective. Nevertheless, it is important to highlight that these women will

require a stricter follow-up period since although rare, premalignant or malignant lesions may be found even in the absence of these factors.

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Table 1 – Clinical characteristics of Women with Endometrial Polyps (n=870)

Characteristics	n	%
Age (n=863)		
< 40 years	27	3.2
40 – 59 years	482	55.8
> 60 years	354	41.0
Menopausal status (n=868)		
Premenopausal	205	23.6
Postmenopausal	663	76.4
Time since menopause (n=578)		
< 10 years	291	50.4
>10 years	287	49.6
Postmenopausal bleeding (n=644)		
Yes	255	39.5
BMI in Kg/m2 (n=852)		
> 30	390	45.7
Parity (n=869)		
0	74	8.6
>1	795	91.4
Use of HT (n=868)		
Yes	61	7.02
Breast Cancer (n=870)		
Yes	137	15.7
Use of Tamoxifen (n=137)		
Yes	102	74.4
Diabetes (n=865)		
Yes	178	20.5
HBP (n=868)		
Yes	505	58.1

Table 2 – Histologic Diagnosis of Endometrial Polyps in the Pre and Postmenopause

Histologic Diagnosis	n	%
Benign		
Endometrial polyp	671	77.1
Polyp with Non-Atypical Simple Hyperplasia	95	10.9
Polyp with Non-Atypical Complex Hyperplasia	5	0.57
Subtotal	771	**88.6**
Premalignant / Malignant		
Polyp with Atypical Simple Hyperplasia	8	0.91
Polyp with Atypical Complex Hyperplasia	6	0.68
Endometrial Carcinoma	22	2.52
Subtotal	36	**4.1**
Others		
Myomas/Secretor/Proliferative/Atrophic	63	**7.3**
Total	870	**100**

Table 3 – Factors Associated with Malignancy in Endometrial Polyps

Characteristics	Benign Polyps (%)	Premalignant/ Malignant Polyps (%)	P value	PR	95%CI
Age (n=863)					
< 40 years	96.3	3.70		1.00	
40 – 59 years	96.8	3.11	0.2623	0.84	(0.12 – 6.13)
> 60 years	94.6	5.36		1.40	(0.20 – 10.42)
Menopausal status (n=868)					
Premenopausal	98.0	1.95	0.0831	2.40	(0.86 – 6.71)
Postmenopausal	95.3	4.67			
Use of Hormone Therapy (n=868)					
Yes	96.7	3.27	1.0000	0.80	(0.20 – 3.26)
No	95.9	4.08			
BMI (n=852)					
< 30	97.1	2.81	0.0383	2.00	(1.02 – 3.93)
> 30	94.3	5.64			
Parity (n=869)					
0	94.5	5.40	0.5305	1.39	(0.50 – 3.82)
>1	96.1	3.89			
Diabetes (n=869)					
Yes	93.8	6.17	0.1050	1.77	(0.88 – 3.54)
No	96.5	3.49			
HBP (n=868)					
Yes	94.8	5.14	0.0486	2.08	(0.98 – 4.38)
No	97.5	2.47			
Breast cancer (n=870)					
Yes	97.8	2.18	0.2340	0.50	(0.16 – 1.62)
No	95.6	4.36			
Use of Tamoxifen					
Yes	99.0	0.98	0.1604	0.17	(0.02 – 1.83)
No	94.2	5.71			
Postmenopausal bleeding (n=644)					
Yes	91.3	8.62	0.0005	3.73	(1.75 – 7.97)
No	97.6	2.31			
Polyp size (n=681)					
< 15mm	97.9	2.09	0.0463	2.41	(0.98 – 5.93)
> 15mm	94.9	5.06			
Postmenop Endometrial Thickness (n=519)					
<5mm	94.3	5.66	0.7202	1.32	(0.41 – 4.29)
>5mm	95.7	4.29			

Table 4 – Factors associated with malignancy in endometrial polyps. Multiple Regression Analysis

Selected Variables	PR	95%CI
Age	1.05	1.01 – 1.09
Postmenopausal bleeding	3.67	1.69 – 7.98

Variables considered: age, time since menopause, use of HT, BMI, parity, DM, HBP, breast cancer, postmenopausal bleeding, endometrial thickness, polyp size

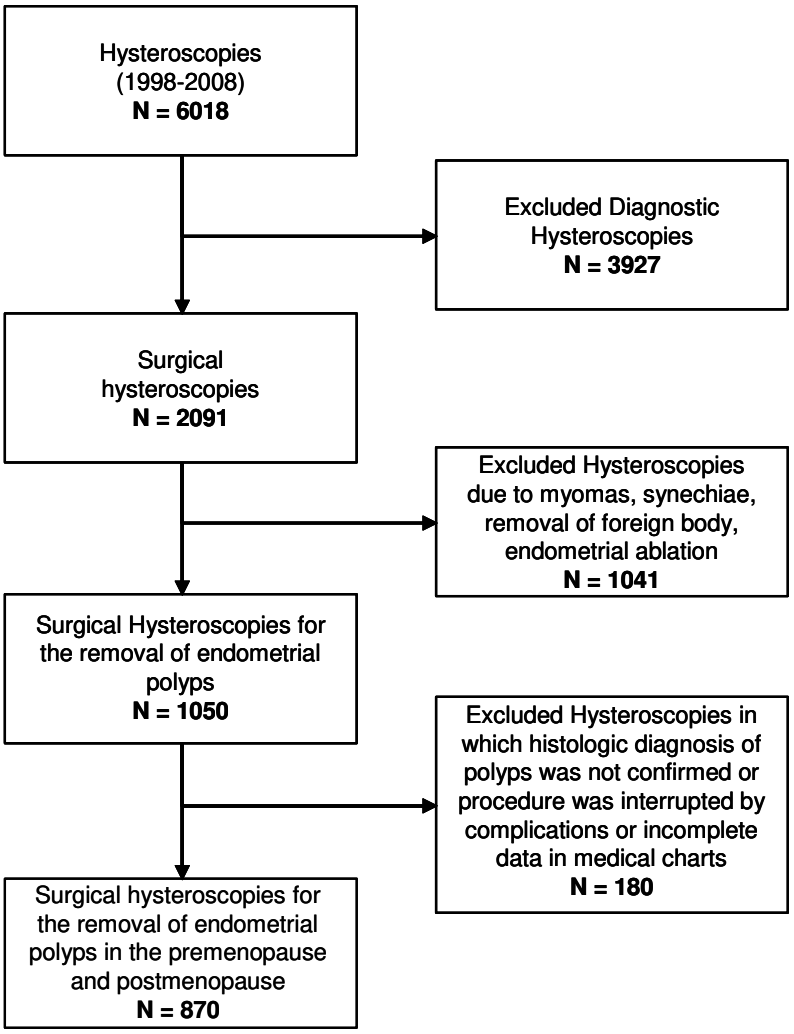

Figure 1 – Flow Chart

3.2. Artigo 2

Accuracy of sonography and hysteroscopy in the diagnosis of premalignant and malignant polyps in postmenopausal women

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Summary

Objective: To evaluate the accuracy of sonographic endometrial thickness and hysteroscopic characteristics in predicting malignancy in postmenopausal women undergoing surgical resection of endometrial polyps. **Subjects and methods:** Five hundred twenty-one (521) postmenopausal women undergoing hysteroscopic resection of endometrial polyps between January 1998 and December 2008 were studied. For each value of sonographic endometrial thickness and polyp size on hysteroscopy, the sensitivity, specificity, positive predictive value and negative predictive value were calculated in relation to histologic diagnosis of malignancy. The best values of sensitivity and specificity for the diagnosis of malignancy were determined by the ROC (Receiver Operating Characteristic) curve. **Results:** Histologic diagnosis identified the presence of premalignancy or malignancy in 4.1% of cases. Sonographic measurement revealed a greater endometrial thickness in cases of malignant polyps when compared to benign and premalignant polyps. On surgical hysteroscopy, malignant endometrial polyps were also larger. An endometrial thickness of 13mm showed a sensitivity of 69.6%, specificity of 68.5%, PPV of 9.3% and NPV of 98% in predicting malignancy in endometrial polyps. Polyp measurement by hysteroscopy showed that for polyps 30mm in size, the sensitivity was 47.8%, specificity was 66.1%, PPV was 6.1% and NPV was 96.5% for predicting cancer. **Conclusions:** Sonographic endometrial thickness showed a higher level of accuracy than hysteroscopic measurement in predicting malignancy in endometrial polyps. Despite this, both techniques were not sufficiently accurate in excluding the need to make a histologic evaluation in suspected cases.

Keywords: *endometrial polyps, endometrial thickness, hysteroscopy, biopsy, accuracy*

1. Introduction

With the routine use of ultrasound in the last 20 years for the investigation of patients with abnormal uterine bleeding or postmenopausal bleeding, the diagnosis of endometrial thickening and endometrial polyp has become more frequent. The prevalence of endometrial polyps ranges from 10 to 40% (1-5) in women with abnormal uterine bleeding. Furthermore, this disorder is found in up to 12% of asymptomatic women in routine gynecologic examinations (6-7).

In postmenopausal women who have risk factors associated with endometrial cancer, such as advanced age, obesity, hypertension, diabetes, tamoxifen use and vaginal bleeding, hysteroscopic polypectomy has been adopted as routine treatment.

There are still doubts about the value of sonographic endometrial thickness which will allow us to predict malignant focal endometrial lesions with a higher level of diagnostic accuracy. Currently, postmenopausal patients with endometrial thickness equal to or greater than 5mm are referred for endometrial biopsy by uterine curettage or surgical hysteroscopy, especially when they had associated vaginal bleeding. In patients with endometrial thickness greater than 12mm, hysteroscopy revealed the presence of endometrial polyps in up to 74.3% of cases (8). In the literature researched, we found no other studies that had assessed the ultrasound value for the prediction of malignancy in focal endometrial lesions.

It is well-known that the malignancy rate associated with endometrial polyps is low. In a meta-analysis carried out by Lee et al (9), it was determined that malignant endometrial polyps were present in 0.8 to 8% of cases, depending on the population studied and the methods used for diagnosis and resection (10-17).

In postmenopausal women, there is a direct relationship between the size of endometrial polyps and the existence of atypical hyperplasia and endometrial carcinoma. A study carried out by Rahimi et al, determined that polyps larger than 1.5cm have a 3.6-fold higher risk of malignancy than lesions with a smaller diameter (15). The aim of this study was to assess the accuracy of sonographic endometrial thickness and hysteroscopic characteristics in predicting malignancy in women undergoing hysteroscopic resection of endometrial polyps using histologic diagnosis as the gold standard.

2. Materials and Methods

From January 1998 to December 2008, 6018 hysteroscopies were performed in the Prof. Dr. José Aristodemo Pinotti Women's Hospital– CAISM/UNICAMP. Of these, all women undergoing hysteroscopic resection of endometrial polyps were selected, using the computerized database from the surgical center, totaling 1050 surgical hysteroscopies (Flow chart annexed).

The clinical, pathological and sonographic data were obtained from medical chart review. This study included 521 postmenopausal women with or without abnormal bleeding who had previously received an ultrasound diagnosis of endometrial polyps, based on findings of focal endometrial thickening associated with the presence of a vascular pedicle. Diagnostic hysteroscopy was performed by using optical systems of 2.8mm (Karl Storz, Germany). For distension of the uterine cavity, CO_2 or saline solution were used. An evaluation of the endocervical canal, endometrial surface, vascularization, tubal ostia; presence of endometrial polyps, myomas or synechiae was made.

Surgical hysteroscopy with the patient under anesthesia was performed by two gynecologic surgeons. For the surgical procedure, a 10-mm resectoscope was used (Karl Storz, Germany). A glycine 1.5% solution was used to distend the uterine cavity. Evaluation of the endocervical canal and endometrial cavity was performed. Resection of endometrial polyps was performed with loop electrocautery that relied on a monopolar electrical current.

Pathologists from the Department of Pathologic Anatomy of the UNICAMP Medical School analyzed the endometrial samples obtained using hematoxylin and eosin staining. Polyps were classified as benign, non-atypical simple hyperplastic, non-atypical complex, atypical simple, atypical complex and malignant.

This study was designed according to recommendations from the questionnaire Quality Assessment of Diagnostic Accuracy Studies (QUADAS) (18) and approved by the Research Ethics Committee of FCM/UNICAMP under number 769/2009.

3. Statistical analysis

Statistical analysis was performed by measurement of rates, means and standard deviations. The sensitivity, specificity, positive predictive value and negative predictive value were calculated for different measures of endometrial thickness and polyp size on hysteroscopy. Histologic diagnosis was used as the gold standard and the cut-off point was established by the methodology for the ROC curve. For statistical analysis, polyps were grouped according to histologic diagnosis into benign (benign polyps, non-atypical simple hyperplastic and non-atypical complex) or premalignant and malignant (atypical simple, atypical

complex and carcinomatous), and the prevalence ratios and their respective confidence intervals were calculated. The significance level was set at 5%. The SAS program version 9.2 was used for these estimates.

4. Results

Five hundred and twenty-one (521) postmenopausal women, mean age of 57.5 years ($\pm$ 10.6) were studied. Mean time since menopause was 12.4 years. There was a sonographic diagnosis of endometrial thickening (>5mm) in 89.8% of cases.

Sonographic measurement of the endometrial thickness in postmenopausal women undergoing hysteroscopic polypectomy, revealed that mean thickness was 11.5mm in benign polyps, 10.5mm in premalignant polyps and 17.4mm in malignant polyps (p=0.002). Of the 16 malignant cases evaluated, 2 had endometrial thickness less than 5mm on sonographic measurement (Table1).

On surgical hysteroscopy, the median size of the benign polyps was 21.5mm, premalignant polyps 24.3mm and malignant polyps 26.3mm (p=0.003) (Table 2).

To predict malignancy, the sensitivity, specificity, positive predictive value and negative predictive value were calculated for each value of sonographic endometrial thickness between 2 and 20mm, resulting in a diagnostic accuracy of 68.6%. The best cut-off point established by the ROC curve was 13mm, showing a sensitivity of 69.6%, specificity of 68.5%, PPV of 9.3% and NPV of 98%. On hysteroscopy, diagnostic accuracy for polyp size was 65.3% and the best cut-off point was 30mm by the ROC curve, with a sensitivity of 47.8%, specificity of 66.1%, PPV of 6.1% and NPV of 96.5% (Table 3 and Figure 1).

With the purpose of determining the risk of malignancy in endometrial polyps according to a group of different risk factors, malignancy risk was calculated in correlation with the presence or absence of postmenopausal bleeding, endometrial thickness greater or less than 13mm and polyp size larger or smaller than 30mm. For patients with vaginal bleeding, endometrial thickness less than 13mm and polyps smaller than 30mm, the risk of malignancy was 14.41 (95% CI 1.85 – 112.57) while for endometrial thickness greater than 13mm and polyps larger than 30mm, the risk was 32.71 (95%CI 3.94 – 271.84). In the absence of postmenopausal bleeding, the assessment of endometrial thickness associated with polyp size did not significantly increase the risk of malignancy (Table 4).

5. Discussion

This study was conducted to evaluate the diagnostic accuracy of sonographic endometrial thickness and hysteroscopic characteristics in predicting malignancy in postmenopausal patients undergoing surgical resection of endometrial polyps. The results showed that accuracy of endometrial thickness was 68.6% and polyp size was 65.3% in the diagnosis of malignancy.

Satisfactory diagnostic methods for the prediction of malignancy in focal endometrial lesions are still lacking and a histologic investigation is required in all suspected cases.

In the postmenopausal period, different cut-off points of endometrial thickness have been proposed to determine whether additional investigation is required, especially in asymptomatic women, where there is a lower risk of malignancy than in women with genital bleeding (18-20). For focal endometrial lesions, in

which the adjacent endometrium has an atrophic pattern, these cut-offs are even less clearly defined. There is little information about the role of sonography as an exclusive method for predicting malignancy in endometrial polyps.

In the present study, ultrasound measurement of endometrial thickness showed that malignant polyps had a higher mean endometrial thickness than that found in the presence of benign polyps. Endometrial thickness measurement of 13mm showed the best sensitivity (69.6%) and specificity (68.5%) in predicting malignancy of endometrial polyps.

According to Dreisler et al, ultrasound made it possible to rule out the presence of benign focal endometrial lesions (polyps or submucous myomas) when endometrial thickness was less than 2.8mm, with a negative predictive value of 98.5% (6). Grimbizis observed a sensitivity of 41.8% and specificity of 83.6% in diagnosing endometrial polyps by ultrasound examination, and were unable to discriminate between benign, premalignant or malignant focal lesions (21).

In a study performed in the United Kingdom with 48.230 women undergoing transvaginal sonography to screen for endometrial cancer not associated with the presence of focal lesions, endometrial thickness of 5.15mm had a sensitivity of 80.5% and specificity of 86.2% in predicting a malignant diagnosis. Using 10 mm cut-offs to define additional investigation of malignancy, the sensitivity was 54.1% and specificity was 97.2% (22).

Among the diagnostic methods for investigating endometrial disease, hysteroscopy has the highest diagnostic efficacy. For hysteroscopic diagnosis of endometrial polyps, a study carried out by Cepni et al, showed a sensitivity of 94% and specificity of 58% (28).

Few studies have evaluated the relationship between size of the polyp and risk of malignancy (15-17, 23). In this study, a measurement of 30mm showed the best sensitivity (47.8%) and specificity (66.1%) in predicting malignancy in endometrial polyps. A meta-analysis conducted to evaluate the oncogenic potential of endometrial polyps in 10.552 patients identified only 8 studies evaluating the association between polyp size and the risk of malignancy (9). In 4 studies, there was an association between larger polyps and a greater risk of malignancy. According to Fernandez-Parra (24), Goldstein (3), Shushan (25) and Gregoriou (26), polyp size did not represent a risk factor for malignancy. The authors highlight that in this meta-analysis polyp size was reported using different units of measurement (centimeters, millimeters or grams) and data were not amenable which have hindered analysis of this association.

The sensitivity attributed to hysteroscopy for any endometrial disease is 86% compared to 54% in ultrasound examination (22). For diagnosis of endometrial hyperplasia and endometrial cancer in the absence of focal lesions, the sensitivity of hysteroscopy was 33% and specificity was 87% (27). Small uterine lesions or functional changes with polypoid pattern in the endometrium may result in failure to identify focal lesions during hysteroscopic evaluation. Furthermore, malignant endometrial neoplasms may coexist with findings of benign endometrial polyps. For this reason, resection of endometrial polyps is recommended in patients at risk, accompanied by guided biopsy of the adjacent endometrium.

6. Conclusion

Data from the present study has shown that sonographic endometrial thickness and hysteroscopic measurement of endometrial polyps have a low level of accuracy in predicting malignancy in focal lesions. These methods alone are not sufficient to exclude the need for additional histologic evaluation in suspected cases. There are still no satisfactory diagnostic methods for identifying which patients should undergo a more judicious surgical resection. Based on the literature, an individual approach of patients with endometrial polyps is recommended, considering a group of risk factors for each patient. Symptomatic postmenopausal women are required to undergo hysteroscopic polyp resection. Asymptomatic postmenopausal women should receive individualized therapy, based on polyp size, presence of risk factors for malignancy, general clinical conditions and their expectations about treatment and risk of malignancy.

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Table 1 - Sonographic endometrial thickness according to histologic diagnosis of endometrial polyp in postmenopausal women (n=519)

Endometrial thickness	Benign N = 495	Premalignant N = 08	Malignant N = 16	p-value*
< 5mm	9%	12%	12%	
5.1 to 10mm	46%	37%	–	
10.1 to 15mm	27%	37%	37%	
15.1 to 20mm	10%	12%	18%	
> 20mm	6%	–	31%	
Mean ± SD	11.5 ± 8.2	10.5 ± 4.7	17.4 ± 8.5	0.002

*Mann-Whitney test

Table 2 – Polyp size by surgical hysteroscopy according to histologic diagnosis of endometrial polyp in postmenopausal women (n=521)

Polyp size	Benign N = 498	Premalignant N = 07	Malignant N = 16	p-value*
< 15mm	38%	28%	25%	
15.1 to 20mm	24%	14%	25%	
20.1 to 25mm	2%	–	6%	
25.1 to 30mm	21%	42%	18%	
> 30mm	12%	14%	25%	
Mean ± SD	21.5 ± 13.9	24.3 ±11.3	26.3 ± 13.2	0.003

*Mann-Whitney test

Table 3 – Accuracy of ultrasound and hysteroscopy in diagnosing malignancy in endometrial polyps in postmenopausal women (n=521)

	Premalignant Malignant	Benign	Sensit (95% CI)	Specif (95% CI)	PPV	NPV	Accuracy	PR (95%CI)
Cut-off point by ROC curve	n	n						
Endometrial thickness								
≥ 13	16	156	69.6%	68.5%	9.3%	98.0%	68.6%	4.61
< 13	7	340	(50.8 a 88.4)	(64.5 a 72.6)				(1.93 – 11)
Total	23	496						
Polyp size								
≥ 30	11	168	47.8%	66.1%	6.1%	96.5%	65.3%	1.74
< 30	12	328	(27.4 a 68.2)	(61.9 a 70.2)				(0.78 – 3.86)
Total	23	496						

Table 4- The risk of malignancy according to postmenopausal bleeding, endometrial thickness and polyp size associated with histologic diagnosis of endometrial polyps in postmenopausal women

Postmenopausal bleeding	Endometrial thickness	Polyp size	Benign	Premalignant and Malignant	PR	95% CI
Present	< 13mm	<30mm	93.7%	6.2%	14.41	1.85 – 112.57
Present	≥ 13mm	≥ 30mm	85.7%	14.2%	32.71	3.94 – 271.84
Absent	<13mm	<30mm	99.5%	0.4%	1.00	–
Absent	≥ 13mm	≥ 30mm	97.3%	2.7%	6.19	0.40 – 96.82

Fisher's Exact test $p<0.0001$

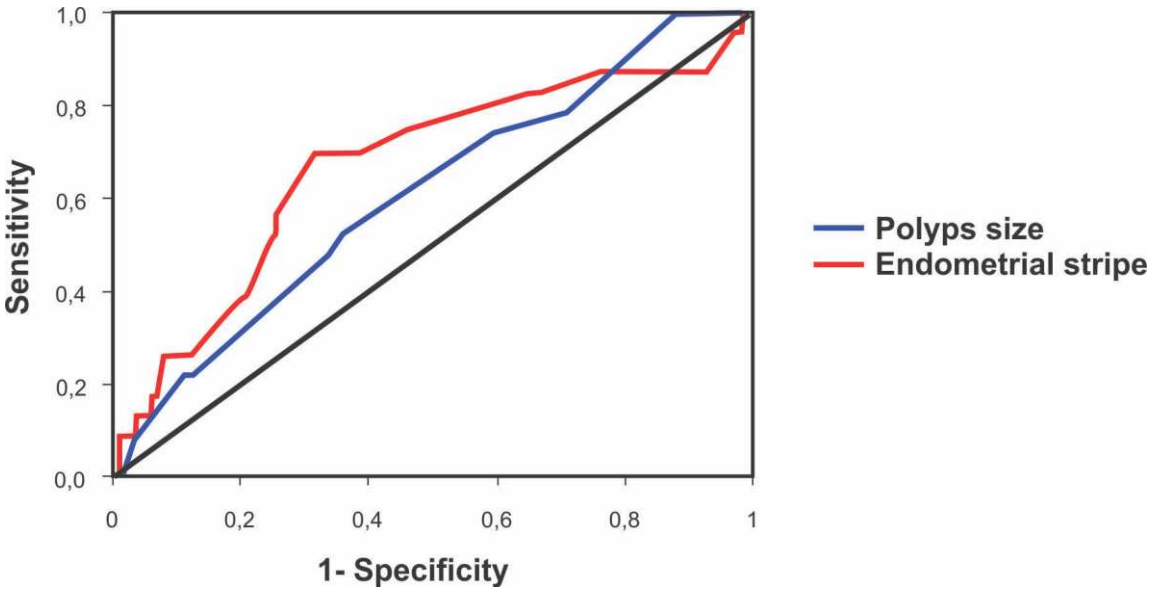

Figure 1 – ROC curve for endometrial polyp size, endometrial stripe and histologic diagnosis of malignancy

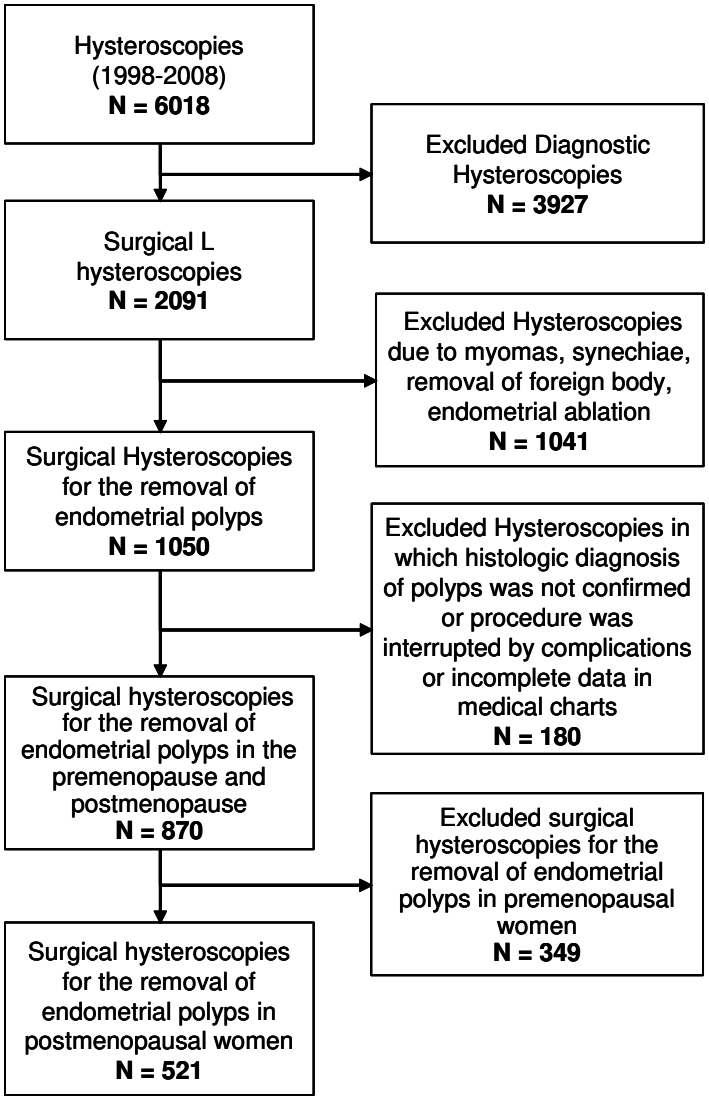

Figure 2 – Flow Chart

4. Discussão

A presença de sangramento vaginal na pós-menopausa, representa importante sintoma observado na prática clínica, motivando diversas consultas médicas e realização de métodos propedêuticos complementares, devido a possibilidade de estarmos diante de um caso de neoplasia maligna endometrial.

A ultrassonografia transvaginal tem sido cada vez mais utilizada na avaliação inicial dessas mulheres. Embora o exame ultrassonográfico de rotina para avaliação endometrial não ser recomendado como screening para câncer de endométrio em mulheres assintomáticas pela maioria das sociedades médicas, muitas vezes pacientes são encaminhadas a serviços de referência após o achado de alterações endometriais, mesmo na ausência de sintomas. Isso tem resultado no aumento progressivo do diagnóstico de pólipos endometriais, em mulheres na pré e na pós-menopausa.

Uma vez encaminhadas, essas mulheres são submetidas à histeroscopia diagnóstica, e os pólipos endometriais representam achado comum. Diante de uma histeroscopia diagnóstica identificando a presença de lesões endometriais focais, essas mulheres são submetidas à ressecção cirúrgica de pólipos sob

anestesia, para diagnóstico histológico. Apesar do baixo risco de malignidade dos pólipos endometriais, que na população estudada foi de 4,1%, e do baixo risco cirúrgico associado à histeroscopia, acrescentam-se riscos significativos ao procedimento pelo fato dessas mulheres serem geralmente idosas e portadoras de diversas comorbidades. Em muitas vezes, o risco atribuído ao procedimento cirúrgico supera o risco de malignidade. Nesta casuística, cerca de 58% eram hipertensas, 45% obesas, 20% diabéticas e 15% com antecedente de câncer de mama.

Apesar desses fatores estarem algumas vezes associados ao maior risco de câncer de endométrio, as análises das razões de prevalência não mostraram associação significativa nos pólipos endometriais avaliados. O sangramento pós-menopausa foi o principal fator de risco associado, com RP de 3,67 (IC95% 1,69 - 7,98). Isso tem motivado a procura de métodos diagnósticos que possam predizer o risco de malignidade, com o objetivo de evitar procedimentos cirúrgicos desnecessários e de alto custo, principalmente em mulheres assintomáticas. A ultrassonografia transvaginal, a histerossonografia e a histeroscopia são amplamente utilizados para esse fim, mas ainda não dispomos de métodos com boa acurácia para predizer malignidade em lesões focais.

Este estudo avaliou o valor diagnóstico da espessura endometrial ultrassonográfica e as características histeroscópicas para predizer malignidade em pacientes submetidas à ressecção cirúrgica de pólipos endometriais na pós-menopausa. Apesar das inúmeras publicações com ultrassonografia e histeroscopia para pesquisa de câncer de endométrio, existem poucos estudos utilizando estes métodos para a avaliação apenas de lesões focais endometriais. Não

encontramos na literatura nenhum estudo que avaliou o papel destes métodos propedêuticos para predizer o risco de malignidade em pólipos endometriais.

No presente estudo, a medida de espessura endometrial para predizer malignidade estabelecido pela curva ROC foi de 13mm e mostrou uma sensibilidade de 69.6%, especificidade de 68,5%, VPP de 9,3% e VPN de 98%. Para o tamanho dos pólipos, o melhor ponto de corte foi de 30mm, com sensibilidade de 47,8%, especificidade de 66,1%, VPP de 6,1% e VPN de 96,5%. Esses dados mostram uma acurácia limitada tanto da ultrassonografia quanto da medida histeroscópica do pólipo para identificar malignidade. Ainda não dispomos de métodos propedêuticos satisfatórios para identificar quais pacientes deveriam ser submetidas à resseção cirúrgica mais criteriosamente.

Embora os pólipos endometriais sejam uma alteração comum e a polipectomia histeroscópica um procedimento largamente utilizado, as recomendações acerca do tratamento variam substancialmente na literatura.

Em mulheres assintomáticas na pós-menopausa, o tratamento deve ser individualizado, baseado no tamanho do pólipo, na presença de marcadores de risco para malignidade, nas condições clínicas gerais e na expectativa das mulheres em relação ao tratamento e ao risco de malignidade. Mulheres sintomáticas na pós-menopausa devem ser submetidas à ressecção dos pólipos para fins terapêuticos e propedêuticos. Futuros estudos visando um maior conhecimento da fisiopatologia e comportamento dos pólipos endometriais através de marcadores imunohistoquímicos poderão contribuir para melhorar as estratégias para intervenção e follow-up mais adequado.

5. Conclusões

– A prevalência de pólipos endometriais pré-malignos e malignos na pré e na pós-menopausa foi de 4,1%.

– O sangramento pós-menopausa e a maior idade foram os fatores clínicos associados ao maior risco de malignidade.

– A linha endometrial de 13mm determinada pela ultrassonografia foi o ponto de corte de maior acurácia para predizer malignidade, com sensibilidade de 69,6% e especificidade de 68,5%.

– A medida histeroscópica dos pólipos endometriais de 30mm apresentou a maior acurácia para predizer malignidade, com sensibilidade de 47,8% e especificidade de 66,1%.

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7. Anexos

7.1. Anexo 1 – Ficha de Coleta de Dados

CAISM-UNICAMP-DEPARTAMENTO DE TOCOGINECOLOGIA

TÍTULO: PREVALÊNCIA DE LESÕES PRÉ-MALÍGNAS E MALÍGNAS EM PÓLIPOS ENDOMETRIAIS DE PACIENTES MENOPAUSADAS ATENDIDAS NO CAISM

No. Estudo: I__I__I__I

Idade: I__I__I anos

Menopausa: I__I, há I__I__I anos **Peri-menopausa**:I__I

Uso de TH: I__I sim I__I não
Se **sim**, há quanto tempo?: I__I__I__I meses
Tipo de TH em uso:_____

Se **não**: I__I nunca usou
I__I já usou antes por I__I__I__I meses e parou há I__I__I__I meses
Tipo de TH em uso:_____

Sangramento pós menopausa: I__Isim I__Inão

Patologias associadas e medicações em uso:

HAS I__I sim I__I não _____

DM I__I sim I__I não _____

Ca de mama I__I sim I__I não uso de tamoxifeno: I__I sim I__I não

_____

_____

Obesidade: **Peso:**I__I__I__I,I__IKG **Altura:**I__I,I__I__Im

A.O.: G__P__A__

Última USG pélvica antes da histeroscopia diagnóstica: ___/___/_____

Diagnóstico: Linha endometrial: I__I__Imm
Pólipo endometrial: I__Isim I__Inão tamanho:I__I__Imm
Outros achados:_____

Indicação da histeroscopia:

I__I espessamento endometrial I__I sangramento pós-menopausa
I__I pólipo endometrial I__I hipermenorragia/metrorragia
I__I conteúdo intra-útero a esclarecer
I__I outros:_____

Histeroscopia diagnóstica : __/___/_____

Canal cervical: I__I normal I__I pólipo endocervical I__I atrófico
I__I outras alterações:_____

Cavidade uterina:

Endométrio: I__I proliferativo I__I secretor I__I atrófico
I__I hipertrófico I__I hipotrófico
Superfície: I__Ilisa I__Ipolipóide I__Icística I__Iirregular
Vascularização: I__Inormal I__Iatípica I__Iausente

Orifícios tubáreos: direito: I__Inormal I__Ivisível I__Ivascularizado
esquerdo: I__Inormal I__Ivisível I__Ivascularizado

Pólipos: I__Iendocervical I__Iendometrial I__Iístmico
I__Icornual I__IOTD I__IOTE

Sinéquias: tipo: I__Imucosa I__Ifibrosa I__Imista
localização: I__Icorporal I__Imarginal I__Icentral múltipla
I__Ifúndica I__Icornual direita I__Icornual esquerda
I__IOTD I__IOTE I__Icérvico-ístmica

DIU: I__I in situ I__Ideslocado I__Ideformado

BE: I__I sim I__I não
Se SIM: I__Iabundante I__Iescassa **AP**:_____
Outros achados:_____

Histeroscopia cirúrgica: __/__/_____ histerometria: I__I__I, I__Icm

cavidade uterina: **tamanho do pólipo**: I__I__Imm

localização: I__Ifúndico I__Iparede lateral D I__Iparede lateral E
I__Iparede anterior I__Iparede posterior I__Iístmico
I__Icornual direito I__Icornual esquerdo

tipo: I__Ipediculado I__Iséssil

superfície do pólipo I__Ilisa I__Iirregular I__Icístico

vascularização: I__Iaumentada I__Itípica I__Iatípica I__Iausente

conduta: polipectomia: I__Isim I__Inão
biópsia de endométrio: I__Isim I__Inão
curetagem uterina: I__Isim I__Inão

anátomo patológico: I__Ipólipo atrófico-cístico
I__Ipólipo da mucosa endometrial
I__Ipólipo atrófico da mucosa endometrial
I__Ipólipo c/ hiperplasia simples
I__Ipólipo c/ hiperplasia complexa s/ atipia
I__Ipólipo c/ hiperplasia simples e focos de atipia
I__Ipólipo c/ hiperplasia complexa e focos de atipia
I__Icarcinoma endometrial I__Iendométrio proliferativo
I__Iendométrio secretor I__Iendométrio atrófico
I__Ioutros achados:_____

7.2. Anexo 2 – Parecer Comissão de Ética em Pesquisa

FACULDADE DE CIÊNCIAS MÉDICAS
COMITÊ DE ÉTICA EM PESQUISA

www.fcm.unicamp.br/pesquisa/etica/index.html

CEP, 22/09/09.
(Grupo III)

PARECER CEP: N° 769/2009 (Este n° deve ser citado nas correspondências referente a este projeto)
CAAE: 0603.0.146.000-09

I - IDENTIFICAÇÃO:

PROJETO: **"EXPRESSÃO DE MARCADORES IMUNO-HISTOQUÍMICOS E RECEPTORES HORMONAIS NO CARCINOMA DE ENDOMÉTRIO E NOS PÓLIPOS ENDOMETRIAIS MALIGNOS E BENIGNOS".**
PESQUISADOR RESPONSÁVEL: Carlos Eduardo de Godoy Junior
INSTITUIÇÃO: CAISM/UNICAMP
APRESENTAÇÃO AO CEP: 01/09/2009
APRESENTAR RELATÓRIO EM: 25/09/10 (O formulário encontra-se no *site* acima)

II - OBJETIVOS

Avaliar a expressão dos marcadores imuno-histoquímicos e receptores hormonais no carcinoma de endométrio e nos pólipos endometriais malignos e benignos.

III - SUMÁRIO

Estudo de corte transversal utilizando-se blocos de parafina arquivados no Departamento de Anatomia Patológica da UNICAMP, de mulheres submetidas à polipectomia histeroscópica entre 1998 e 2008, cujo anátomo-patológico diagnosticou pólipo endometrial maligno. Estes casos serão comparados a igual numero de casos de pólipos endometriais benignos e carcinoma de endométrio não associado à presença de pólipos. Estima-se que haverá cerca de 30 casos em cada grupo. Serão avaliadas a expressão de marcadores imuno-histoquímicos bcl-2, p53, Ki-67, COX-2, aromatase e receptores de estrógeno e progesterona. A técnica de TMA será feita no Hospital do Câncer e as reações imuno-histoquímicas no Laboratório de Patologia Experimental do CAISM. Análise estatística: Será realizada análise dos dados através de análise uni-variada com cálculo de freqüências, médias e desvio-padrão. A comparação das variáveis dependentes (RE, RP, COX-2, aromatase, Ki-67, p53 e Bcl-2) entre os grupos, será feita através do teste de qui-quadrado ou exato de Fisher. Para estes cálculos será utilizado o programa SAS versão 9.01. Para esses procedimentos estatísticos será utilizado o Programa Statistical Analises System (SAS) versão 0.1.

IV - COMENTÁRIOS DOS RELATORES

Trata-se de projeto de Mestrado onde serão estudados pólipos endometriais benignos e malignos no carcinoma de endométrio e avaliação da expressão de marcadores imuno-histoquímicos e receptores de estrógeno e progesterona nestes pólipos. O tema estudado é de relevância, pois acredita-se que os resultados desta pesquisa poderão trazer subsídios para futuros estudos focados no tratamento de algumas lesões endometriais e para a indicação mais criteriosa da polipectomia histeroscópica em pacientes na pós-menopausa.. O projeto está bem redigido, o desenho do estudo é

adequado, apresenta critérios de inclusão e exclusão bem definidos. A metodologia a ser empregada está bem descrita. Os aspectos éticos estão adequadamente abordados.

V - PARECER DO CEP

O Comitê de Ética em Pesquisa da Faculdade de Ciências Médicas da UNICAMP, após acatar os pareceres dos membros-relatores previamente designados para o presente caso e atendendo todos os dispositivos das Resoluções 196/96 e complementares, resolve aprovar sem restrições o Protocolo de Pesquisa, a dispensa do Termo do Consentimento Livre e Esclarecido, bem como todos os anexos incluídos na pesquisa supracitada.

O conteúdo e as conclusões aqui apresentados são de responsabilidade exclusiva do CEP/FCM/UNICAMP e não representam a opinião da Universidade Estadual de Campinas nem a comprometem.

VI - INFORMAÇÕES COMPLEMENTARES

O sujeito da pesquisa tem a liberdade de recusar-se a participar ou de retirar seu consentimento em qualquer fase da pesquisa, sem penalização alguma e sem prejuízo ao seu cuidado (Res. CNS 196/96 – Item IV.1.f) e deve receber uma cópia do Termo de Consentimento Livre e Esclarecido, na íntegra, por ele assinado (Item IV.2.d).

Pesquisador deve desenvolver a pesquisa conforme delineada no protocolo aprovado e descontinuar o estudo somente após análise das razões da descontinuidade pelo CEP que o aprovou (Res. CNS Item III.1.z), exceto quando perceber risco ou dano não previsto ao sujeito participante ou quando constatar a superioridade do regime oferecido a um dos grupos de pesquisa (Item V.3.).

O CEP deve ser informado de todos os efeitos adversos ou fatos relevantes que alterem o curso normal do estudo (Res. CNS Item V.4.). É papel do pesquisador assegurar medidas imediatas adequadas frente a evento adverso grave ocorrido (mesmo que tenha sido em outro centro) e enviar notificação ao CEP e à Agência Nacional de Vigilância Sanitária – ANVISA – junto com seu posicionamento.

Eventuais modificações ou emendas ao protocolo devem ser apresentadas ao CEP de forma clara e sucinta, identificando a parte do protocolo a ser modificada e suas justificativas. Em caso de projeto do Grupo I ou II apresentados anteriormente à ANVISA, o pesquisador ou patrocinador deve enviá-las também à mesma junto com o parecer aprovatório do CEP, para serem juntadas ao protocolo inicial (Res. 251/97, Item III.2.e)

Relatórios parciais e final devem ser apresentados ao CEP, de acordo com os prazos estabelecidos na Resolução CNS-MS 196/96.

VII – DATA DA REUNIÃO

Homologado na IX Reunião Ordinária do CEP/FCM, em 22 de setembro de 2009.

Prof. Dr. Carlos Eduardo Steiner
PRESIDENTE do COMITÊ DE ÉTICA EM PESQUISA
FCM / UNICAMP