RESEARCH ARTICLE

Which Endometrial Pathologies Need Intraoperative Frozen Sections?

Gulsah Balik*, Mehmet Kagitci, Isık Ustuner, Funda Akpinar, Emine Seda Guvendag Guven

Abstract

Background: Endometrial cancers are the most common gynecologic cancers. Endometrial sampling is a preferred procedure for diagnosis of the endometrial pathology. It is performed routinely in many clinics prior to surgery in order to exclude an endometrial malignancy. We aimed to investigate the accuracy of endometrial sampling in the diagnosis of endometrial pathologies and which findings need intra-operative frozen sections. Materials and Methods: Three hundred nine women applying to a university hospital and undergoing endometrial sampling and hysterectomy between 2010 and 2012 were included to this retrospective study. Data were retrieved from patient files and pathology archives. Results: There was 17 patients with malignancy but endometrial sampling could detect this in only 10 of them. The endometrial sampling sensitivity and specificity of detecting cancer were 58.8% and 100%, with negative and positive predictive values of 97.6%, and 100%, respectively. In 7 patients, the endometrial sampling failed to detect malignancy; 4 of these patients had a preoperative diagnosis of complex atypical endometrial hyperplasia and 2 patients had a post-menopausal endometrial polyps and 1 with simple endometrial hyperplasia. Conclusions: There is an increased risk of malignancy in post-menopausal women especially with endometrial polyps and complex atypia hyperplasia. Endometrial sampling is a good choice for the diagnosis of endometrial pathologies. However, the diagnosis should be confirmed by frozen section in patients with post-menopausal endometrial polyps and complex atypia hyperplasia .

Keywords: Complex atypical hyperplasia - endometrial sampling - endometrial pathologies - frozen section

Asian Pac J Cancer Prev, **14 (10)**, 6121-6125

Introduction

Uterine cancer is the most common gynecologic malignancy in the United States with an approximately 1 in 40 lifetime risk for women. The American Cancer Society estimates for endometrial cancer in the United States for 2013 are about 49,560 new cases (uterine corpus cancers) per year (American Cancer Society, 2006). Therefore, once hysterectomy is planned, endometrial sampling is a preferred procedure for diagnosis of the endometrial pathology (Stovall et al., 1989). The purpose of this procedure is to exclude an endometrial malignancy. The dilatation curettage has traditionally been considered as standard for the investigation of the endometrial pathology. The lesions can be benign, premalignant or malignant (Stovall et al., 1989; Dijkhuizen, 2000). Benign pathologies include fibroids and polyps. Premalignant pathologies are endometrial hyperplasia with or without atypia.

Endometrial hyperplasia is defined as abnormal proliferation of the uterine endometrial glands and often results in abnormal uterine bleeding (Indermaur et al., 2007). Women with endometrial hyperplasia have an elevated risk of endometrial carcinoma (Bilgin et al., 2004). Endometrial polyp (EMP) is a common benign disease of the uterus. But, postmenopausal women with EMP are at an increased risk of malignancy, compared to premenopausal women (Hileeto et al., 2005).

Hysterectomy is the most frequently performed operation in gynecology (Farquhar et al., 2002). Most of the hysterectomies have benign indications. These indications are myoma uteri, pelvic organ prolapse, endometriosis, adenomyosis, abnormal uterine bleeding, chronic pelvic pain, infection and cancer. Frozen section is used in differentiating tumor grade, myometrial invasion, and cervical extension of the tumor in gynecologic operations (Morotti et al., 2012). If there is any doubt in the preoperative diagnosis of the patient, frozen section can be helpful to make the diagnosis. We cannot perform frozen section for every patient.

Thus, there is an important question waiting to be answered. Which patients should be evaluated by frozen section? We aimed to investigate the accuracy of endometrial sampling in the diagnosis of endometrial pathologies and the findings needing intra operative frozen sectioning.

*Obstetrics and Gynecology, Medicine, Recep Tayyip Erdogan Univercity , Rize, Turkey *For correspondence: gulsahbalik@gmail.com*

Materials and Methods

This study was retrospectively performed between 2010 and 2012 at a university hospital. We planned a retrospective comparison of the histopathological diagnosis on endometrial sampling and the hysterectomy specimens. A total of 309 patients with any gynecological pathology, who underwent endometrial sampling and were treated by hysterectomy within a year of the diagnosis, were included in the study. Sampling method for diagnosis was pipelle biopsy in twenty-five patients, and fractional dilation and curettage (D&C) for the remaining patients.. Age, hysterectomy indications, preoperative endometrial sample findings and postoperative hysterectomy specimen results were obtained from patient files and pathology reports. Final pathological evaluations were compared with endometrial sampling results.

Classification by histological type, grade and stage was based on the criteria adopted by the Federation International of Gynecology and Obstetrics (FIGO) for endometrial carcinoma (Creasman, 2009). The classification of endometrial hyperplasia was according to the 2003 WHO criteria.

The data were analyzed by using SPSS (Statistical Package for Social Sciences) 17.0 for Windows. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the endometrial sampling were calculated. Ethical approval for the study was obtained from the hospital's Research and Development Committee.

Results

The study had a total of 309 subjects. The mean age of the patients was 49.4 years with a range of between 32 and 83 years. A hundred and thirty-eight (44.7%) patients were menopausal. Indications for hysterectomy are shown in Table 1.

The preoperative results of the endometrial sampling of the patients and the final pathological diagnosis are shown at Table 2.

There were 299 patients with benign endometrial pathologies diagnosed by endometrial sampling but this was revised to benign pathologies in 292 (98.3%) patients and malignancy pathologies in 7 (20.8%) patients on final pathology. The number of patients with malignancy diagnoses by endometrial sampling (n: 10) remained the same by final pathology. (Table 3). The endometrial sampling sensitivity and specificity of detecting cancer were 58.8% and 100%, with negative and positive predictive values of 97.6%, and 100%, respectively.

In 7 patients, the endometrial sampling failed to detect malignancy; 4 of these patients had a preoperative diagnosis of complex atypical endometrial hyperplasia (CAEH), 2 patients had a post menopausal EMP, and 1 with simple endometrial hyperplasia. Preoperative endometrial pathology results and the final pathology results of all malign patients are compared in Table 3.

Table 1. The Hysterectomy Indications of Patients

Indications	Cases % (n)	
Abnormal uterine bleeding	14.6	(45)
Leiomyomas	47.6	(147)
Endometrial hyperplasia	6.1	(19)
Endometrial polyps	3.9	(12)
Endometrial carcinoma	2.3	(7)
Ovary cyst	12.3	(38)
Pelvic infection	2.3	(7)
Pelvic organ prolapse	5.2	(16)
Cervical pathology	2.9	(9)
Chronic pelvic pain	1	(3)
Postmenopausal bleeding	1.9	(6)

Table 2. Concordance Rate of Pre and Post Operative Histopathology

	Endometrial sampling n (%)	Hysterectomy specimen n (%)
Proliferative endometrium	81(26.2)	95(30.7)
Secretory endometrium	74 (23.9)	72(23.3)
Basal endometrium	26(8.4)	31(10)
Atrophic endometrium	24(7.8)	26(8.4)
Endometrial polyp	61(19.7)	47(14.5)
Simple atypia	16(5.2)	11(3.6)
Complex atypia	8(2.6)	1(0.3)
Adenosarcoma	1(0.3)	2(0.6)
Carcinoma	9(2.9)	15(4.9)
Chronic endometrit	9(2.9)	9(2.9)

Table 3. The Comparation of Preoperative Endometrial Sampling and Final Diagnosis in Malign Cases

Case	Age	Presenting Symptom	Endometrial Sampling	Final Diagnosis
1	46	Vaginal discharge	Simple atypia	Adenosarcoma
2	82	Postmenopausal bleeding	Adenosarcoma	Adenosarcoma
3	65	Postmenopausal bleeding	Carcinoma	Carcinoma
4	49	Chronic pelvic pain	Endometrial polyp	Carcinoma
5	64	Postmenopausal bleeding	Endometrial polyp	Carcinoma
6	69	Vaginal discharge	Complex atypia	Carcinoma
7	57	Postmenopausal bleeding	Complex atypia	Carcinoma
8	50	Postmenopausal bleeding	Complex atypia	Carcinoma
9	56	Postmenopausal bleeding	Complex atypia	Carcinoma
10	57	Postmenopausal bleeding	Carcinoma	Carcinoma
11	83	Postmenopausal bleeding	Carcinoma	Carcinoma
12	62	Postmenopausal bleeding	Carcinoma	Carcinoma
13	56	Postmenopausal bleeding	Carcinoma	Carcinoma
14	52	Postmenopausal bleeding	Carcinoma	Carcinoma
15	51	Postmenopausal bleeding	Carcinoma	Carcinoma
16	48	Postmenopausal bleeding	Carcinoma	Carcinoma
17	50	Chronic pelvic pain	Carcinoma	Carcinoma

Discussion

Endometrial carcinoma is one of the three most common malignancies of the female genital tract (Dijkhuizen et al., 2000). Abnormal uterine bleeding is one of the most frequent problems in adult women (American Cancer Society, 2006). There are various benign reasons for abnormal uterine bleeding. But, uterine bleeding is the most common symptom of endometrial cancer. Preoperative endometrial histopathological examination is carried out in some clinics either by D&C or office endometrial sampling for patients with planned hysterectomy (Stovall et al., 1989). In a recent meta-analysis of endometrial sampling methods, the

sensitivity for detection of endometrial carcinoma was in the range of 25-100%, while the specifity varied between 93% and 100% (Dijkhuizen et al., 2000). In the studies of Demirkiran et al. (2000) it was shown that the pipelle biopsy and D&C showed almost equal sensitivity in the diagnosis of endometrial pathologies. Both are no adequate methods for focal endometrial pathologies (Demirkiran et al., 2012). Stovall and colleagues reported D&C to miss 7% (2/30) of endometrial cancers (Stovall et al., 1989). Gundem et al. (2003) also reported that the correlation between preoperative and postoperative endometrial histopathological findings was statistically insignificant (Gundem et al., 2003). On the contrary, other studies reported that there is a statistically significant correlation between preoperative and postoperative endometrial histopathological findings. The study of Saygılı et al. showed that endometrial pathology findings positively correlated with postoperative hysterectomy pathology results in women with postmenopausal bleeding (Saygili, 2006). In our study a strong correlation was found in benign and malign diagnosis between endometrial sampling and final pathologic results. However, an inconsistency was detected in the CAEH diagnoses. Thus, we think that the diagnoses should be confirmed by frozen sectionsin patients with CAEH.

The most common reason for post menopausal uterine bleedings is benign while 10% is malign. Most malignancy cases are found in women aged 50 and over, with more than half of all endometrial cancer cases diagnosed in the 50-69 age group. Uterine bleeding is the presenting sign in more than 90% of postmenopausal patients with endometrial carcinoma (Newell, 2012). Causes of premenopausal and postmenopausal bleeding include: endometrial carcinoma; cervical carcinoma; vaginal atrophy; endometrial hyperplasia +/- polyp; cervical polyps; hormone-producing ovarian tumors; haematuria and rectal bleeding (Epstein et al., 2011; Newell, 2012). Thus, all pre- and post-postmenopausal vaginal bleedings must be investigated to identify the cause and exclude malignancy. The incidence of vaginal bleeding of malign patients was 76% in our study.

Endometrial hyperplasia is an increased growth of the endometrium. Mild or simple hyperplasia is the most common type and has a very small risk of becoming cancerous. If the hyperplasia is "atypical," it has a higher chance of becoming a cancer. Endometrial hyperplasia is a precursor to endometrioid adenocarcinoma (Lax, 2011). It is typically diagnosed by endometrial biopsy or curettage when a woman is noted as suffering from abnormal uterine bleeding particularly in older women. Endometrial hyperplasia is classified into 4 different categories: simple hyperplasia with or without cytological atypia and complex hyperplasia with or without cytological atypia (Bilgin et al., 2004; Indermaur et al., 2007). Atypical endometrial hyperplasia has been strongly associated with endometrial carcinoma. The rate of progression to endometrial carcinoma has been estimated to be 0-3% in patients without atypia, 0-8% in patients with simple atypical hyperplasia, and 9-29% in patients with CAEH. AEH is a well-known precursor to endometrial cancer and 23-30% of patients with AEH will progress to cancer (Kurman, 1985). The histopathological diagnosis of AEH is difficult (Zaino et al., 2006). Morotti et al. (2012) reported that frozen section effeciently identified the cases that diagnosed with AEH on endometrial biopsy (Morotti et al., 2012). Antonsen et al founded that 59% of women diagnosed preoperatively with AEH had cancer, and one in three of these patients had a high-risk cancer requiring full staging procedure (Antonsen et al., 2012). Frozen section analysis of hysterectomy specimens in patients with atypical endometrial hyperplasia was found to be necessary to determine the presence of cancer and the need for surgical staging in a different study (Gundem et al., 2003). Bilgin et al. (2004) reported that frozen section has a low accuracy rate to excluding the possibility of endometrial cancer in patients with preoperative diagnosis of CAEH (Bilgin et al., 2004). In several studies, it was reported that the underlying adenocarcinoma rate was 47.8% in patients with a preoperative diagnosis of CAEH (Lambert et al., 1994; Valenzuela et al., 2003). The risk of concomitant endometrial carcinoma has been reported to be 20-59% in CAEH (Kurman et al., 1985; Kendall et al., 1998). Tavassoli and Kraus found that the risk of adenocarcinoma is 25% in patient with CAEH (Tavassoli, 1978). Therefore, all women diagnosed with AEH should be handled by specialized gynecological oncologists able to do the necessary surgery, and evaluated by pathologists who have special interest and experience in evaluating endometrial samples with cancer and/or hyperplasia. In the present study malignancy was detected in 4 patients with CAEH and simple hyperplasia in 1 patient.

Endometrial polyp is a benign lesion composed of endometrial glands and stroma forming a circumscribed mass that protrudes into the endometrial cavity. The pathogenesis and natural history of endometrial polyps are not very clear. It has three types: benign (atrophic, functional), hyperplastic and cancerous (Savelli et al., 2003). The prevalence of EP is between 6% and 32% (Dreisler et al., 2009). The incidence of EP increases with age. Endometrial polyps rarely become malignant, but hyperplastic changes are more common. The uterine EP has a potential risk of developing malignant tumors especially in postmenopausal women. Tamoxifen administration following breast cancer treatment may result in the development of endometrial intraepithelial neoplasia associated with an EP (Carlson, 2008). There is a risk factor for a concomitant endometrial pathology (hyperplasia, sarcoma, and carcinoma) in postmenopausal endometrial polyps. Savelli et al. found that malignancy potential of EP is 0.8% (Savelli et al., 2003). Anastasiadis et al. (2000) in studying of 126 endometrial polyp cases s, found that 94 were benign, 30 were with premalignant changes (complex and atypical hyperplasias) and 2 had undergone malignant degeneration (Anastasiadis et al., 2000). Malignant degeneration of endometrial polyps was observed only in postmenopausal women Goldstein et al. (2002) demonstrated that the rate of malignant degeneration of an endometrial polyp was 4.8% (Goldstein et al., 2002). Hileeto and colleagues reported that malignancy potential of EP increases with age and it gets higher after 65 years (Hileeto et al., 2005). On the contrary; the study of Perri et al. (2010) suggests that EP

is not a cancer precursor (Perri et al., 2010). In the study of Pavia et al, the risk of malignancy in EP was higher in women with postmenopausal bleeding and advanced age (Costa-Paiva et al., 2011). There is not a consensus of malignancy potential of the EP, which is reported to be in the range of 0.5-13%, in the literature. Thus, especially atypical focal endometrial lesions should be removed completely with H/S and histological assessment must be carried out (Costa-Paiva et al., 2011; Litta., 2013). Every endometrial polyp should be resected. Two of our 49 and the 68 years old post-menopausal patients were diagnosed with EP by endometrial sampling, which was subsequently found to be endometrial carcinoma with frozen section. Frozen section and careful examination of full endometrial cavity should be done in patients with post menopausal EP to rule out possible malignancies. .

Myoma uteri is the most frequent indication for hysterectomies performed for benign conditions. Preoperative endometrial sampling has not proven to be of any benefit in myoma uteri. The malignancy risk of myoma uteri is 13.4% and 1.1% for postmenopausal and premenauposal women, respectively. Bohman et al. (1988) also reported that endometrial carcinoma was 5.5 times more common in postmenopausal patients with myoma and uterine bleeding in comparison to the analogous group of patients in the reproductive period (Bokhman et al., 1988). In another study, endometrial sampling is recommended before hysterectomy only in patients older than 35 years old with abnormal bleeding and postmenopausal vaginal bleeding (Stovall et al., 1989). In our study 47.6% (n: 147) of the hysterectomies were done for myoma uteri and endometrial carcinoma was not detected in any these patients either preoperatively or postoperatively.

The incidence of coexisting EP is 56.8% in the postmenopausal women with cervical polyp (Coeman et al., 1993). In another study, this figure was 26.9% (Vilodre et al., 1997). Routine excision of the cervical polyps is recommended regardless of symptomatology and simultaneous endometrial evaluation with histopathologyc examination should be done (Coeman et al., 1993; Vilodre et al., 1997). In our clinic we routinely perform endometrial sampling in patient with cervical polyps.

Frozen section (FS) evaluation usually aims to rule out the presence of malignancy and assesses the cases with malignancy for staging (Acs, 2002). In the literature, studies on the accuracy of FS are limited. Some studies reported low accuracy rate of FS (Morotti et al., 2012). The accuracy of FS is reported in the range of 80-96.5% in high risk uterine pathologies (Coffey et al., 2005; Salman et al., 2009). Peroperative endometrial sampling for frozen section is rarely done. But, peroperative endometrial sampling can be done to evaluate endometrium if there is any doubt of malignancy in benign cases especially in fibromas.

Since the distinction of CAEH and well differentiated adenocarcinoma is difficult in frozen sections, the final diagnosis can be done after paraffin bloc section examination (Quinlivan et al., 2001; Coffey et al., 2005). FS examination is necessity to avoid incomplete surgery in CAEH, although it is not a good predictor to rule out endometrial cancer in CAEH. Therefore, we routinely use FS analysis to all CAEH in our clinic.

In conclusion, there is an increased risk of malignancy in post menopausal women especially with endometrial polyp and complex atypia hyperplasia. The phycians may have confidence in endometrial sampling in the diagnosis of benign and malign cases. But the diagnoses must be confirmed by frozen section in patients with CAEH and especially post menopausal EP.

Acknowledgements

No potential conflict of interest relevant to this article was reported.

References

Acs G (2002). Intraoperative consultation in gynecologic pathology. *Semin Diagn Pathol*, **19**, 237-54.

Anastasiadis PG, Koutlaki NG, Skaphida PG, et al (2000). Endometrial polyps: prevalence, detection, and malignant potential in women with abnormal uterine bleeding. *Eur J Gynaecol Oncol*, **21**, 180-3.

Antonsen SL, Ulrich L, Hogdall C (2012). Patients with atypical hyperplasia of the endometrium should be treated in oncological centers. *Gynecol Oncol*, **125**, 124-8.

Bilgin T, Ozuysal S, Ozan H, et al (2004). Coexisting endometrial cancer in patients with preoperative diagnosis of atypical endometrial hyperplasia. *J Obstet Gynaecol Res*, **30**, 205-9.

Bokhman Ya, Tkeshelashvili VT, Vishnevsky AS, Volkova AT (1988). Myoma uterus as a marker of oncogynecological pathology in preand post-menopause. *Eur J Gynaecol Oncol*, **9**, 355-9.

Carlson JW, Mutter GL (2008). Endometrial intraepithelial neoplasia is associated with polyps and frequently has metaplastic change. *Histopathol*, **53**, 325-32.

Coffey D, Kaplan AL, Ramzy I (2005). Intraoperative consultation in gynecologic pathology. *Arch Pathol Lab Med*, **129**, 1544-57.

Costa-Paiva L, Godoy CE Jr, Antunes A Jr, et al (2011). Risk of malignancy in endometrial polyps in premenopausal and postmenopausal women according to clinicopathologic characteristics. *Menopause*, **18**, 1278-82.

Coeman D, Van Belle Y, Vanderick G, De Muylder X, De Muylder E (1993). Hysteroscopic findings in patients with a cervical polyp. *Am J Obstet Gynecol*, **169**, 1563-5.

Creasman W (2009). Revised FIGO staging for carcinoma of the endometrium. *Int J Gynaecol Obstet*, **105**, 109.

Demirkiran F, Yavuz E, Erenel H, et al (2012). Which is the best technique for endometrial sampling? Aspiration (pipelle) versus dilatation and curettage (D&C). *Arch Gynecol Obstet*, **286**, 1277-82.

Dijkhuizen FP, Mol BW, Brölmann HA, Heintz AP (2000). The accuracy of endometrial sampling in the diagnosis of patients with endometrial carcinoma and hyperplasia. *Cancer*, **89**, 1765-72.

Dreisler E, Stampe Sorensen S, Ibsen PH, Lose G (2009). Prevalence of endometrial polyps and abnormal uterine bleeding in a Danish population aged 20-74 years. *Ultrasound Obstet Gynecol*, **33**, 102-8.

Epstein E, Ramirez A, Skoog L, Valentin L (2001). Dilatation and curettage fails to detect most focal lesions in the uterine cavity in women with postmenopausal bleeding. *Acta Obstet Gynecol Scand*, **80**, 1131-6.

Goldstein SR, Monteagudo A, Popiolek D, Mayberry P, Timor-Tritsch I (2002). Evaluation of endometrial polyps. *Am J Obstet Gynecol*, **186**, 669-74.

Gundem G, Sendag F, Kazandi M (2003). Preoperative and postoperative correlation of histopathological findings in cases of endometrial hyperplasia. *Eur J Gynaecol Oncol*, **24**, 330-3.

Hileeto D, Fadare O, Martel M, Zheng W (2005). Age dependent association of endometrial polyps with increased risk of cancer involvement. *W J Surg Oncol*, **3**, 8.

Farquhar C, Steiner CA (2002). Hysterectomy rates in the United States. *Obstet Gynecol,* **99**, 229-34.

Indermaur M, Shoup B, Tebes S (2007). The accuracy of frozen pathology at time of hysterectomy in patients with complex atypical hyperplasia on preoperative biopsy. *Am J Obstet Gynecol*, **196**, 40-2.

Kendall BS, Ronnett BM, Isacson C, et al (1998). Reproducibility of the diagnosis of endometrial hyperplasia, atypical hyperplasia, and well-differentiated carcinoma. *Am J Surg Pathol*, **22**, 1012-9.

Kurman RJ, Kaminski PF, Norris HJ (1985). The behavior of endometrial hyperplasia. A long term study of 'untreated' hyperplasia in 170 patients. *Cancer*, **56**, 403-12.

Lambert B, Muteganya D, Lepage Y, et al (1994). Complex hyperplasia of the endometrium: predictive value of curettage vs. hysterectomy specimens. *J Reprod Med*, **39**, 639-42.

Lax S (2011). Precursor lesions of endometrial carcinoma: diagnostic approach and molecular pathology. *Pathologe*, **32**, 255-64.

Litta P, Bartolucci C, Saccardi C, et al (2013). Atypical endometrial lesions: hysteroscopic resection as an alternative to hysterectomy. *Eur J Gynaecol Oncol*, **34**, 51-3.

Morotti M, Menada MV, Moioli M, et al (2012). Frozen section pathology at time of hysterectomy accurately predicts endometrial cancer in patients with preoperative diagnosis of atypical endometrial hyperplasia. *Gynecol Oncol*, **125**, 536-40.

Newell S, Overton C (2012). Postmenopausal bleeding should be referred urgently, **256,** 13-5.

Quinlivan JA, Petersen RW, Nicklin JL (2001). Accuracy of frozen section for the operative management of endometrial cancer. *BJOG*, **108**, 798-803.

Perri T, Rahimi K, Ramanakumar AV, et al (2010). Are endometrial polyps true cancer precursors? *Am J Obstet Gynecol*, **203**, 232.

Salman MC, Usubutun A, Dogan NU, Yuce K (2009). The accuracy of frozen section analysis at hysterectomy in patients with atypical endometrial hyperplasia. *Clin Exp Obstet Gynecol*, **36**, 31-4.

Savelli L, De Iaco P, Santini D, et al (2003). Histopathologic features and risk factors for benignity, hyperplasia and cancer in endometrial polyps. *Am J Obstet Gynecol*, **188**, 927-31.

Saygili H (2006). Histopathologic correlation of dilatation and curettage and hysterectomy specimens in patients with postmenopausal bleeding. *Eur J Gynaecol Oncol*, **27**, 182-4.

Stovall TG, Solomon SK, Ling FW (1989). Endometrial sampling prior to hysterectomy. *Obstet Gynecol*, **73**, 405-9.

Surico N, Viale S, Crivello T, Amedeo MC, Porcelli A (1988). How many endometrial cancer may develop from hyperplasia? *Panminerva Med*, **30**, 225-30.

Valenzuela P, Sanz JM, Keller J (2003). Atypical endometrial hyperplasia: grounds for possiblem is diagnosis of endometrial adenocarcinoma. *Gynecol Obstet Invest*, **56**, 163-7.

Vilodre L-CF, Bertat R, Petters R, Reis FM (1997). Cervical polyp as risk factor for hysteroscopically diagnosed endometrial polyps. *Gynecol Obstet Invest*, **44**, 191-5.

Zaino RJ, Kauderer J, Trimble CL, et al (2006). Reproducibilityof the diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. *Cancer*, **106**, 804-11.