

Abstract of the PhD thesis:

## **THE ROLE OF MINIMALLY INVASIVE DIAGNOSTIC METHODS IN ABNORMAL UTERINE BLEEDING**

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**Introduction:** Abnormal uterine bleeding (AUB) is the most frequent cause of visits for gynecologic conditions in the whole gynecologic pathology. Endometrial cancer (EC) ranks alongside ovarian cancer as the leading types of gynecological cancer. Early diagnosis of EC is almost entirely dependent on the prompt recognition and evaluation of AUB. Consequently, the main goal of investigations in AUB is exclusion of EC.

**Objectives:** The aim of the study was to determine the accuracy and diagnostic performance of different methods for investigating the endometrium (Papanicolaou smear, transvaginal ultrasound, Pipelle biopsy and uterine curettage) in diagnosing EC. The main objective was to determine the diagnostic performance of Pipelle endometrial biopsy as an outpatient procedure, with the main focus on diagnosing EC, by comparing it to the „gold standard” dilatation and curettage (D&C). Furthermore, other objectives were to determine and quantify the risk factors for EC in patients with AUB, as well as to measure the level of discomfort caused by the two methods of endometrial biopsy.

**Design and methods:** From the patients presenting spontaneously or referred to the 1st Obstetrics and Gynecology Clinic of Târgu Mureş for the symptom of AUB, between January 2010 and September 2011, a total of 123 women were enrolled in this study. For determining and quantifying the risk factors for EC the design chosen was a hospital-based case-control study. Case patients were defined as women diagnosed with EC, control subjects were women with benign endometrial histology. Each patient enrolled in the study, after signing the written consent and completion of the clinician-completed form, had a cervical smear. This was followed by the measurement of endometrial thickness (ET) by transvaginal ultrasound scan (TVUS) after which the Pipelle biopsy and D&C were performed. After completion of biopsy procedures, women were asked to complete a visual-analogue scale (VAS) to measure the level of discomfort caused by the two methods. A prospective, blind, comparative study was conducted to determine the diagnostic performance of the Pipelle device. In cases where subsequent hysterectomy was performed, we used the histology results from the hysterectomy specimens to determine the final histology, and to evaluate the performance of Pipelle biopsy and D&C in comparison with this.

**Results:** The median age of the patients included in the study was 53.0 years (min. 30, max. 80 years). 56.1% of the patients were postmenopausal. The risk factors of increasing age, postmenopausal status, arterial hypertension, diabetes mellitus, history of gallbladder disease,

history of menstrual irregularities and/or PCOS, family and/or personal history of EC related cancers and increasing number of total risk factors present were significantly associated with EC. There was a statistically significant difference ( $P < .001$ ) between the ET of patients diagnosed with EC ( $n = 28$ ) and the patients diagnosed with benign endometrial pathology ( $n = 91$ ): 19.3 mm (SD = 7.43 mm; min. 7 mm; max. 40 mm) and 10.41 mm (SD = 5.88; min. 2 mm; max. 30 mm), respectively. The overall sensitivity and the negative predictive value of TVUS was 100%. The prevalence of abnormal cervical cytology did not differ significantly among the two groups ( $P = .186$ ), and the sensitivity and positive predictive value of Pap smear for EC was extremely low (4.16% and 6.25%, respectively). The insertion failure rate through the cervical canal of the Pipelle device was 4.06%. In 6 cases (4.87%) the Pipelle procedure failed to obtain an adequate tissue sample for histological analysis. In 114 cases (92.68%), both methods (Pipelle and D&C) obtained a sufficient and adequate tissue sample for histology. In 64.91% of cases the Pipelle histology results were in agreement with the histology results yielded by the D&C. The histology results from D&C and hysterectomy specimen (40 cases) were compared to determine the final histology. The calculated Kappa value for overall agreement between Pipelle and final histology of .652 ( $p < .001$ ) showed substantial to moderate agreement between the two methods. If we accept the diagnosis of complex atypical hyperplasia with suspicion of invasion as positive for endometrial cancer, the sensitivity, specificity and predictive values of the Pipelle method in diagnosing EC was 100%. The performance of the Pipelle in diagnosing endometrial polyps (sensitivity 56.67%, false negative rate 43.33%) and functional/dysfunctional endometrium (sensitivity 58.06%, false negative rate 41.94%) was poor. In comparison with the histology results from the hysterectomy specimens, the sensitivity of D&C in detecting EC was 95.63%. The most frequent type of endometrial cancer was endometrioid type adenocarcinoma (48.15%). The predictive value of the histological grade of EC cases assigned to Pipelle and D&C samples was identical: 82.35%. The mean pain score measured on the VAS during Pipelle biopsy was 28.41 (SD = 15.48; min. 1, max. 60) and was significantly less ( $p < .001$ ) than the pain experienced during D&C: 74.59 (SD = 17.23; min. 32, max. 100). All subjects would have preferred the Pipelle biopsy instead of D&C, if they had to undergo another endometrial biopsy in the future.

**Conclusions:** The presence or absence of risk factors for EC does not justify limiting further investigation of the endometrium to certain subgroups of the population. ET measurement through TVUS is especially useful in postmenopause to exclude EC, as a thin, clear endometrial echo in a patient with postmenopausal bleeding has a very high negative predictive value. Conventional cervical cytology has a very poor predictive value for EC and has no role in evaluation of patients with AUB. The accuracy of Pipelle was comparable with that of D&C in detecting EC and predicting the histological grade of EC. However, it was only moderately accurate in detecting other benign lesions of the endometrium, especially endometrial polyps. In comparison with D&C, the Pipelle biopsy caused significantly less pain, was more acceptable to patients, required no anesthesia, and was not associated with any complications. Pipelle sampling combined with ET measurement by TVUS can be considered an acceptable, less invasive alternative method, which could significantly reduce the number of D&Cs performed.

**Key words:** abnormal uterine bleeding, biopsy, cancer, endometrium, risk factors, Pipelle, Papanicolaou smear, transvaginal ultrasound scan, visual-analogue scale.