Ultrasound in the management of women with post-menopausal bleeding

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To the memory of my father Leopold

ABSTRACT

The aim of this thesis was to investigate how ultrasound can be used in the diagnostic work-up of women with post-menopausal bleeding (PMB) to optimise and individualise their management.

The thesis is based on six studies comprising post-menopausal women *with* (Study I-VI) and *without* (Study VI) abnormal bleeding. The clinical value of conventional ultrasound, with or without saline infusion (hydrosonography), and of power Doppler ultrasound, was determined, and the performance of different endometrial biopsy techniques was compared and correlated with sonographic findings.

Re-bleeding and endometrial growth were common during a follow-up period of 12 months in women with PMB and endometrium < 5 mm, irrespective of whether dilatation and curettage (D&C) was carried out or not. Endometrial pathology was only found in women with endometrial growth to ≥ 5 mm. If these women are managed by ultrasound follow-up, endometrial sampling should be performed if the endometrium grows to a thickness of ≥ 5 mm, and perhaps also in cases of re-bleeding. Endorette® (a simple endometrial sampling device) and D&C had similar diagnostic value in women with PMB and endometrium < 7 mm, whereas D&C was superior to Endorette® in women with endometrium ≥ 7 mm. However, in another study on women with PMB and endometrium ≥ 5 mm, we found that D&C failed to diagnose about half of the focal lesions in the uterine cavity that were removed by operative hysteroscopy. Thus, the presence or absence of focal lesions should determine the diagnostic procedure. Hydrosonography was found to be as good as hysteroscopy with regard to detecting focal lesions, but neither method was accurate enough in discriminating benign from malignant lesions. Distension difficulties at hydrosonography were more common in women with endometrial cancer and should therefore raise a suspicion of malignancy. A multivariate logistic regression model including clinical information, conventional ultrasound variables, and power Doppler variables seems to be superior to endometrial ultrasound morphology in correctly diagnosing endometrial cancer in cases where the endometrium measures 5–15 mm. The reproducibility of endometrial measurements allows reliable discrimination between post-menopausal women with endometrium < 5 mm and ≥ 5 mm.

Keywords: Endometrial cancer, endometrial pathology, endometrial polyp, malignancy, post-menopausal bleeding, ultrasound, endometrial biopsy, curettage, saline contrast sonohysterography (SCSH), hydrosonography, hysteroscopy, power Doppler, reproducibility, observer variation, endometrium

CONTENTS

LIST OF PAPERS

The following six papers upon which this thesis is based are referred to in the text by their Roman numerals:

I Epstein E, Valentin L. Re-bleeding and endometrial growth in women with post-menopausal bleeding and endometrium < 5 mm managed by dilatation and curettage or ultrasound follow-up. A randomised controlled study. *Ultrasound in Obstetrics and Gynecology* 2001;18:499-504

II. Epstein E, Skoog L, Valentin L. Comparison of Endorette[7] and dilatation and curettage for sampling of the endometrium in women with post-menopausal bleeding. *Acta Obstetrica et Gynecologica Scandinavica* 2001; 80:959-64

III. Epstein E, Ramirez R, Skoog L, Valentin L. Dilatation and curettage fails to detect most focal lesions in the uterine cavity in women with post-menopausal bleeding *Acta Obstetrica et Gynecologica Scandinavica* 2001; 80:1131-6

IV. Epstein E, Ramirez R, Skoog L, Valentin L. Transvaginal sonography, saline contrast sonohysterography and hysteroscopy for the investigation of women with post-menopausal bleeding and endometrium ≥ 5 mm. *Ultrasound in Obstetrics and Gynecology* 2001;18:157-62

V. Epstein E, Skoog L, Isberg PE, Olofsson PÅ, De Smet F, De Moor B, Gudmundsson S, Valentin L. An algorithm including results of grey scale

and power Doppler ultrasound examination to predict endometrial malignancy in women with post-menopausal bleeding. *Submitted*

VI. Epstein E, Valentin L. Reproducibility of endometrial measurements in post-menopausal women. *Submitted*

ABBREVIATIONS

BMI = Body Mass Index

CAH = Complex Atypical Hyperplasia

CI = Confidence Interval

D&C = Dilatation and Curettage

HRT = Hormone Replacement Therapy

Intra-CC = Intra-class correlation coefficient

Inter-CC = Inter-class correlation coefficient

MIEIUM = Mean Intensity of Pixels in the Endometrium

MIVA = Mean Intensity of Pixels in the Vascularized Area

MP = Menopause

OR = Odds Ratio

PI = Pulsaltility Index

PMB = Post-menopausal Bleeding

RI = Resistance Index

ROC-curve = Receiver Operator Characteristic-curve

RR = Relative Risk

SCSH = Saline Contrast Sonohysterography same as hydrosonography (i.e., instillation of saline into the uterine cavity during scanning)

TVS = Transvaginal Sonography

3D = Three Dimensional

DEFINITIONS

Post-menopausal woman As defined in this thesis, a woman reporting a period of at least 12 months of amenorrhea after the age of 40 years, where such amenorrhea was not attributable to medication or disease.

Post-menopausal bleeding (PMB) As defined in this thesis, any vaginal bleeding in a post-menopausal woman not on hormone replacement therapy (HRT), or unscheduled bleeding in a post-menopausal woman on HRT.

BACKGROUND

The state of knowledge as of 1995, when the studies in this thesis were planned, is presented.

Introduction

Approximately 70% of all gynaecological consultations in post-menopausal women are related to abnormal vaginal bleeding. Women with PMB must be examined because 10%–14% have endometrial cancer (Danero et al. 1986, Conoscenti et al. 1995, Karlsson et al. 1995). Transvaginal ultrasound can be used to discriminate between normal and pathological endometrium if endometrial thickness ≥ 5 mm is used to indicate pathology (Karlsson et al. 1995). It has been suggested that it might be reasonable to refrain from endometrial sampling in women with PMB and endometrium < 5 mm (Karlsson et al. 1995) because the risk of endometrial cancer in these women is very low (< 1%) (Cacciatore et al. 1994, Karlsson et al. 1995, Van den Bosch et al. 1995) and the risk of any endometrial pathology is only 6%–16% (Cacciatore et al. 1994, Conoscenti et al. 1995, Karlsson et al. 1995). Omitting endometrial sampling in women with PMB and endometrium < 5 mm could save money, inconvenience for the patient, and possibly decrease patient morbidity. However, the consequences of expectant management have not been examined.

Approximately 50% of women with PMB have an endometrium measuring ≥ 5 mm at ultrasound examination (Karlsson et al. 1995). In women with PMB and endometrium ≥ 5 mm, endometrial sampling should be performed because 60% of these women have pathological endometrium (Karlsson et al. 1995) and approximately 20% have endometrial cancer (Karlsson et al. 1995). In women with a thick endometrium who are at high risk of endometrial pathology, a reliable

diagnostic method is mandatory. Outpatient endometrial sampling devices have become very popular because they can save time, money, and patient morbidity if used as a first-step investigation tool in women with PMB. New devices are continually being developed. However, they should not be recommended unless their diagnostic properties have been thoroughly examined. Simple sampling devices like Pipelle® might miss a large proportion of endometrial polyps and even endometrial hyperplasia (Reid et al. 1993, Van den Bosch et al. 1995). There are, to the best of my knowledge no studies evaluating the result of simple sampling devices in relation to the sonographic findings. Could ultrasound help us to select women in whose case simple devices could be safely used? Traditionally, dilatation and curettage (D&C) has been the method of choice to obtain an endometrial sample. However, there are studies indicating that D&C may frequently miss endometrial pathology (Valle 1981, Gimpelson and Rappold 1988, Stovall et al. 1989), especially focally-growing lesions (Gimpelson and Rappold 1988), even though the extent of the problem in women with PMB needs to be further investigated. Moreover, there are studies indicating that hyperplasia and perhaps endometrial polyps are risk factors for developing endometrial carcinoma (Sherman and Brown 1979, Kurman et al. 1985, Pettersson et al. 1985). Therefore, D&C might not be the best method of investigating women with PMB, unless focally growing lesions (such as polyps) can be excluded.

Various techniques can be used in the diagnostic work-up of women with PMB to exclude focal lesions in the uterine cavity. Diagnostic hysteroscopy is known to be an accurate method of disclosing focally-growing pathological lesions in the uterine cavity (Valle 1981, Loffer 1989). At conventional ultrasound examination such lesions, may be suspected (Atri et al. 1994, Cicinelli et al. 1994) but confirmation by saline infusion (hydrosonography) might improve the accuracy (Parsons and Lense

1993, Cicinelli et al. 1994, Gaucherand et al. 1995). However, the accuracy of hydrosonography in disclosing focal lesions in women with PMB has not been elucidated.

A reliable estimate of the probability of endometrial carcinoma could help us to optimise the timing of an endometrial biopsy procedure, or even make us refrain from further invasive diagnostic procedures such as D&C or hysteroscopy in women at high operative risk. Ultrasound can be used in different ways to estimate the risk of endometrial cancer. First, this risk increases with increasing endometrial thickness (Karlsson et al. 1995). Second, endometrial morphology at grey scale ultrasound might be suggestive of endometrial cancer (Sheth et al. 1993, Atri et al. 1994, Hulka et al. 1994). However, the accuracy of conventional ultrasound and hydrosonography in differentiating between benign and malignant lesions in women with PMB, based on endometrial morphology, have not been prospectively evaluated. Third, some studies have shown that colour Doppler ultrasound of the uterine and subendometrial arteries can differentiate between benign and malignant endometrium (Bourne et al. 1991, Kurjak et al. 1993), while other studies found a substantial overlap in Doppler results between benign and malignant lesions, limiting the clinical usefulness of colour Doppler (Chan et al. 1994, Sladkevicius et al. 1994, Sheth et al. 1995). Finally, power Doppler is a very recent and promising ultrasound technique that has a high ability to visualise tortuous, irregular vessels. This makes it an appealing technique for detecting and characterising intratumoural vessels (Jain et al. 1991, Rubin et al. 1994). However, the clinical utility of power Doppler in discriminating benign from malignant endometrium needs to be determined.

There are few articles on the reproducibility of endometrial measurements in post-

menopausal women. Karlsson and co-workers (1994) found that the mean difference in endometrial thickness measurements between five inexperienced examiners and one experienced examiner in women with PMB was 1.5 mm. However, it is questionable if it is correct to consider the measurements taken by an experienced observer to represent the "truth". More studies on the reproducibility of endometrial measurements in post-menopausal women, focusing on the reproducibility of measurements around the 5 mm cut-off point are needed.

Endometrial cancer

Endometrial cancer is the third most common cancer among Swedish women, and the ninth leading cause of death from malignancy ("Statistics Sweden"). Overall, 2%–3% of all women will develop endometrial cancer during their lifetime (Berek 1996). Most cancers (70%–80%) present in stage I (i.e., when the cancer is confined to the uterine body). The five-year survival rate for stage I malignancy is 75%–95% (Berek 1996). Approximately 90% of women with endometrial carcinoma have vaginal bleeding as their only presenting symptom (Berek 1996). Several risk factors for the development of endometrial carcinoma have been identified. Among these are nulliparity (relative risk [RR] 2–3), late menopause (RR 2.4), obesity (RR 3–10), diabetes mellitus (RR 2.8), unopposed oestrogen therapy (RR 4–8), Tamoxifen (RR 2–3), and atypical endometrial hyperplasia (RR 8–29) (Berek 1996).

Precursors of endometrial carcinoma

Endometrial hyperplasia may precede or occur simultaneously with endometrial carcinoma. The risk of endometrial hyperplasia progressing to endometrial carcinoma is related to the presence and severity of cytological atypia. The frequency of hyperplasia progressing to endometrial carcinoma is reported to be

1%–9% in women with simple hyperplasia, 3%–22% in women with complex hyperplasia, and 29%–57% in women with complex atypical hyperplasia (Sherman and Brown 1979, Kurman et al. 1985). Approximately 25% of patients with atypical hyperplasia detected at endometrial sampling (D&C or simple sampling devices) will have an associated endometrial carcinoma at hysterectomy (Berek 1996).

Endometrial polyps may also be associated with endometrial carcinoma, even though the association is less well established. Petterson and co-workers (1985) found that 20% of all women who developed endometrial carcinoma had polyps in a previous curettage specimen vs. 10% of the controls (odds ratio [OR] = 3.4, 95% confidence interval [CI] = 1.3–9.3).

Cervical cancer

Studies from Sweden show that 0.8%-1.3% of all women with PMB have cervical carcinoma (Gredmark et al. 1995, Karlsson et al. 1995). In the study by Karlsson and co-workers (1995) comprising 1,168 women, the prevalence of cervical cancer was 0.4% in women with endometrium < 5 mm and 1% in women with endometrium ≥ 5 mm. It is important one note that the prevalence of cancer of the cervix among women with PMB differs between countries/regions. In South East Asia, cervical cancer is a more common cause of PMB than endometrial cancer, the prevalence of cervical cancer being 5%–13% among women with PMB (Lin et al. 1993, Lee et al. 1995).

Preoperative diagnostic methods to assess endometrial abnormalities

Ultrasound measurement of endometrial thickness

Several studies have assessed the accuracy of transvaginal sonography in detecting endometrial malignancy or endometrial abnormalities. Some of these studies included only a few women with cancer, and different thresholds for endometrial thickness to indicate malignancy were used, making comparisons difficult. Until a meta-analysis is performed, we must rely on the largest study undertaken to date, a multicenter study comprising 1,168 women with PMB (Karlsson et al. 1995). The prevalence of endometrial abnormalities was found to increase with increasing endometrial thickness (Karlsson et al. 1995). At a cut-off of 4 mm (endometrium > 4 mm indicating endometrial abnormality), the sensitivity with regard to detecting histologically abnormal endometrium was 96% and the specificity 68%; the corresponding figures, if a cut-off of 5 mm, was used were 94% and 78%, respectively. Using the 5 mm cut-off, 2 cancers were missed, whereas none were missed using the 4 mm cut-off (Karlsson et al. 1995).

Ultrasound assessment of endometrial morphology

In three retrospective studies on post-menopausal women, an association was found between cystic spaces within the endometrium and endometrial polyps, and between inhomogeneous, poorly-defined endometrium and cancer (Sheth et al. 1993, Atri et al. 1994, Hulka et al. 1994). However, cystic changes were seen in 76% of those women presenting with benign conditions manifesting with endometrial thickening compared to in 24% of women with endometrial malignancies, indicating that these findings were not specific (Atri et al. 1994). In

the majority of endometrial malignancies, the endometrial contour was poorly defined, but 40% of the cases manifested well-defined endometrial border (Atri et al. 1994). In one study of 35 post-menopausal women with endometrial cancer, the endometrium had an inhomogeneous appearance in 45% of the cases, a hyperechoic appearance in 45%, and a hypoechoic appearance in 10% (Kurjak et al. 1993). An interruption of the subendometrial halo was consistent with myometrial invasion (Kurjak et al. 1993). The findings in the retrospective studies cited indicate that there are overlapping features between benign and malignant conditions, limiting the clinical usefulness of endometrial morphology. Further, prospective study using pre-determined criteria for various lesions is therefore needed to evaluate the utility of endometrial morphology.

Hydrosonography

Parson and Lense first described hydrosonography (infusion of saline into the uterine cavity during scanning) in 1993. In a retrospective analysis, Dubinsky and co-workers (1995) described polyps as having a homogeneous echogenicity and a pedunculated attachment to the uterine wall that does not interrupt the endometrial lining, whereas submucous myomas showed more heterogeneous echogenicity and had a more sessile attachment. The accuracy of hydrosonography in detecting focal lesions and correctly making a specific diagnosis of endometrial polyp among 43 pre-menopausal women was analysed retrospectively (Cicinelli et al. 1994). Hydrosonography had a sensitivity of 79% and a specificity of 100% in detecting focal lesions, and a sensitivity of 58% and a specificity of 100% in diagnosing endometrial polyps (Cicinelli et al. 1994). However, this study (Cicinelli et al. 1994), did not include women with endometrial cancer. Therefore, the accuracy of hydrosonography in discriminating between benign and malignant lesions could not be determined.

Colour Doppler

Several investigators have suggested the use of colour Doppler measurements of uterine, subendometrial, or endometrial arteries to improve the accuracy of transvaginal sonography in diagnosing endometrial abnormalities in women with PMB. However, the results of these studies and the conclusions drawn are conflicting. Kurjak and co-workers (1993) detected blood flow in the endometrium in 91% of women with endometrial cancer, as compared to 8% of those with hyperplasia, and none of those with normal endometrium. The mean resistance index (RI) in the endometrial vessels was significantly lower in women with endometrial cancer than in those with hyperplasia. Bourne and co-workers (1991) conducted a study on 138 selected post-menopausal women. They found that the pulsatility index (PI) in the uterine arteries was significantly lower in women with endometrial cancer than in those without, and that Doppler velocimetry (PI < 1.5) was superior to endometrial thickness (> 10 mm) in correctly diagnosing endometrial carcinoma (sensitivity 100% vs. 83%, specificity 99% vs. 95%) (Bourne et al. 1991). As opposed to the findings above, Chan and co-workers (1994) found that colour Doppler gave no additional information as compared to conventional ultrasound in disclosing malignancy. Sheth and co-workers (1995) found an overlap between the PI and RI in the endometrial vessels of benign and malignant lesions. They carefully evaluated the histological specimens in 16 women (10 malignant, 6 benign) and found that thin-walled vessels, that lacked smooth muscle (characterising neovascularisation) were seen in both benign (polyps) and malignant lesions (Sheth et al. 1995). Finally, Sladkevicius and co-workers (1994) reported endometrial thickness to be a better method than Doppler velocimetry (in endometrial, subendometrial, and uterine arteries) in discriminating between benign and malignant, or normal and pathological, endometrium in women with PMB.

Power Doppler ultrasound

The Power Doppler ultrasound image displays the intensity of the Doppler shift spectrum and reflects the number of red blood cells flowing in the vessel (Dymling et al. 1991). To some extent it reflects the velocity of the flow, but does not indicate the direction of the flow at all. Power Doppler ultrasound has a higher sensitivity to slow flow than colour Doppler ultrasound; it is relatively angle independent, and does not aliase (Rubin et al. 1994). It also has a better ability to demonstrate tortuous, irregular vessels, which makes power Doppler a promising technique for detecting and characterising intratumoural vessels (Jain et al. 1991, Rubin et al. 1994). The disadvantages of power Doppler are that it is very sensitive to motion artefacts and dependent on the distance between the organ and the transducer (Rubin et al. 1994).

Endometrial biopsy techniques

D&C

Traditionally, D&C has been the method of choice for obtaining an endometrial sample. However, there are studies indicating that the use of D&C as the 'golden standard' in the investigation of PMB should perhaps be questioned, especially in women with focal lesions in the uterine cavity. As early as 1957, Englund and co-workers reported that the uterine cavity was satisfactorily emptied in only 35% of women undergoing D&C. In two studies comprising both pre- and post-menopausal women with abnormal uterine bleeding, 40%–90% of polyps and 43%–66% of hyperplasias were missed by D&C (Valle 1981, Stovall et al. 1989). In a retrospective study comprising women of all ages undergoing routine D&C before hysterectomy, Stovall (1989) and colleagues reported that D&C missed endometrial cancer in 7% (2/30) of the cases.

Outpatient biopsy techniques, Pipelle®, Endorette®

In recent years, simple and inexpensive outpatient endometrial sampling devices like Pipelle[7] (Prodimed, Neuilly en Thelle, France) or Endorette[7] (Medscand AB, Malmö, Sweden) have been advocated. Both the well-known Pipelle[7] and the recently-developed Endorette[7] are endometrial sampling devices consisting of a piston sliding within a flexible plastic sheath. Pipelle[7] has one hole at its tip; Endorette[7] has four. The accuracy of Endorette[7] has not yet been investigated. However, Pipelle[7] sampling has been reported to fail in 1%–21% of women with PMB (Batool et al. 1994, Van den Bosch et al. 1995), and miss as many as 90% of polyps and submucous myomas, 36% of hyperplasias (Van den Bosch et al. 1995), and 40% of atypical hyperplasias (Reid et al. 1993). The sensitivity of Pipelle[7] in detecting endometrial cancer in post-menopausal women was 94% in three studies

comprising 16 malignancies (3,7, and 6, respectively) (Reid et al. 1993, Batool et al. 1994, Van den Bosch et al. 1995). The number of cancers is too small for a reliable estimation of the accuracy of Pipelle[7] in diagnosing endometrial cancer.

Operative hysterocopy

Diagnostic hysteroscopy is an old method of examining the uterine cavity. It was introduced by Abunasis as early as 1864 using an air system and an external light source. As reported by Neuwrith and Amin (1976), operative hysteroscopy has been successfully used since 1976, to remove intracavitary lesions. Several studies have compared the accuracy of diagnostic D&C to that of hysteroscopic resection and have found that D&C was less revealing in 9%–83% of the cases (Valle 1981, Gimpelson and Rappold 1988, Loffer 1989).

OBJECTIVES

The aim of this thesis is to evaluate how transvaginal ultrasound may be used in the management of women with PMB, the final goal being to enable optimal and individual diagnostic work-up and treatment. Specifically, these objectives were:

- to compare the frequency of re-bleeding and endometrial growth during a 12 month follow-up period between women with PMB and endometrium < 5 mm managed by D&C, and those followed by ultrasound (Study I).
- to compare the diagnostic properties of Endorette[7] with those of D&C in relation to endometrial thickness in women with PMB (Study II).
- to determine the ability of transvaginal ultrasound and hydrosonography to detect focally-growing lesions in the uterine cavity, and to determine the ability of transvaginal ultrasound, hydrosonography, and hysteroscopy to discriminate between polyps and endometrial cancer (Study III).
- to determine the prevalence of focally-growing lesions in the uterine cavity in women with PMB and endometrium ≥ 5 mm, and the extent to which such lesions can be diagnosed and removed by D&C (Study IV).
- to determine whether power Doppler ultrasound of the endometrium could contribute to a correct diagnosis of endometrial malignancy in women with PMB and endometrium ≥ 5 mm (Study V).
- to determine intra- and inter-observer reproducibility of ultrasound measurements of endometrial thickness in post-menopausal women (Study VI).

PATIENTS/SUBJECTS

Informed consent was obtained from all women after the procedures had been fully explained to them. The number of women included in each study, their ages, time elapsed since menopause, and their use of HRT are shown in Table 1. The patients in studies I-V comprised consecutive women presenting at the clinic with PMB. Those in study VI comprised both asymptomatic post-menopausal women and women with PMB. All women were examined between April 1995 and April 2001 at the ultrasound unit of the department of Obstetrics and Gynaecology at the University Hospital, Malmö.

Table 1. Patients

Study	Number of women	Age in years Median (range)	Years past MP* Median (range)	HRT** n (%)	Estriol or vaginal Estradiol, n (%)
Study I					
Ultrasound group	48	62 (48-89)	10 (1-45)	20 (42%)	8 (17%)
D&C group	49	65 (49-89)	15 (1-48)	15 (31%)	11 (22%)
Study II	133	65 (46-91)	15 (1-42)	41 (31%)	31 (23%)
Study III and IV	105	66 (43-88)	16 (1-47)	28 (27%)	22 (21%)
Study V	83	66 (43-86)	17 (1-47)	26 (31%)	19 (23%)
Study VI	53	68 (49-92)	-	10 (19%)	7 (13%)

*MP = menopause

**HRT = hormone replacement therapy

METHODS

The Ethics Committee of the Medical Faculty at Lund University, Sweden, has approved of all studies.

Ultrasound equipment

The equipment used was an Acuson 128XP ultrasound system with a 4.5 to 7 MHz transducer (Studies I and II), a Sequoia Ultrasound system with a 5 to 8 MHz transvaginal transducer (Studies III-VI) (Acuson, Inc., Mountainview, CA, USA), and an ATL ultrasound system with an 8 MHz transvaginal transducer (Study VI) (Advanced Technology Laboratories, Philips Medical Systems, Bothell, Washington, USA).

Techniques for pre-operative evaluation of the endometrium

General ultrasound

Transvaginal ultrasound examination was performed with the woman in the lithotomy position. The bladder was emptied before the examination. All ultrasound examinations were performed by E. Epstein or L. Valentin. The results of conventional ultrasound examinations were documented on hard copies. The results of hydrosonographies and the power Doppler ultrasound examinations were documented on videotapes and hard copies.

Endometrial measurements

All measurements were done with callipers on a frozen ultrasound image. The thickness of the endometrium was measured from a longitudinal sonogram through the thickest area of the endometrium, and from the outermost border of the endometrium on one side to that on the other side. Thus, the measurements of endometrial thickness included both endometrial layers and any expansive process or fluid in the endometrial cavity (Figure 1). Endometrial measurements were classified in full millimetres (Study I-VI). Thus, measurements of 0-4.4 mm were classified as '< 5 mm' and measurements of 4.5 mm or more as '≥ 5 mm'. The same was applied in Study II, i.e., measurements of 0-6.4 mm were classified as '< 7 mm' and measurements of 6.5 mm or more as '≥ 7 mm' (Study II).

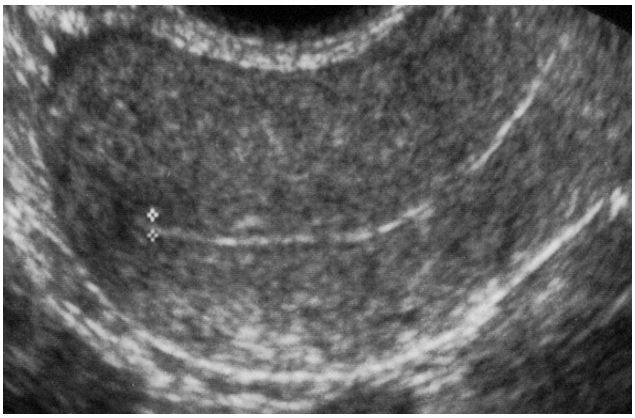


Figure 1. Measurement of endometrial thickness

Hydrosonography

In Study IV, hydrosonography was performed immediately after the completion of the conventional ultrasound examination. No premedication or prophylactic antibiotics before the examination were used before the examination. A Kremer de la Fontaine catheter, which is a double-lined transparent polyethylene catheter with an outer diameter of 2.1 mm and an inner diameter of 1.7 mm (5 Fr.) without an inflatable balloon, was used. The main part of the catheter is fairly rigid, while the protruding inner lining forms a flexible tip with two opposite distal side ports. A 20 ml syringe was attached to the catheter, which was flushed with sterile saline before it was inserted through the cervical canal and advanced to the uterine fundus. Five to 10 ml of saline were usually required to distend the cavity. In case of a patulous cervix, more fluid was continuously infused to overcome the back flow. During saline infusion, the uterine cavity was re-evaluated by transvaginal ultrasound in both longitudinal and a transverse planes (Figure 2).

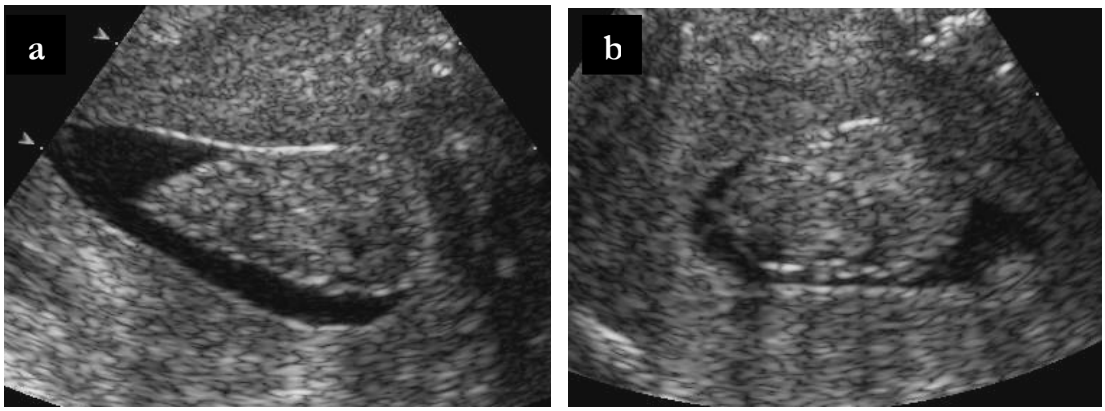


Figure 2. (a) hydrosonography, lognitudial sonogram; (b) hydrosonography, transversal sonogram

Endometrial morphology at ultrasound examination

In Study IV, the endometrium was classified as to endometrial polyp, submucous myoma, and malignancy by the ultrasound examiner, using predetermined criteria. In Study V the endometrium was classified as either malignant or benign, using the same criteria of malignancy, as follows:

Endometrial malignancy was suspected on the basis of an irregular endometrial/myometrial border, an inhomogeneous endometrial texture at conventional ultrasound examination, or an irregular surface facing the uterine cavity at hydrosonogarphy (Figure 3).

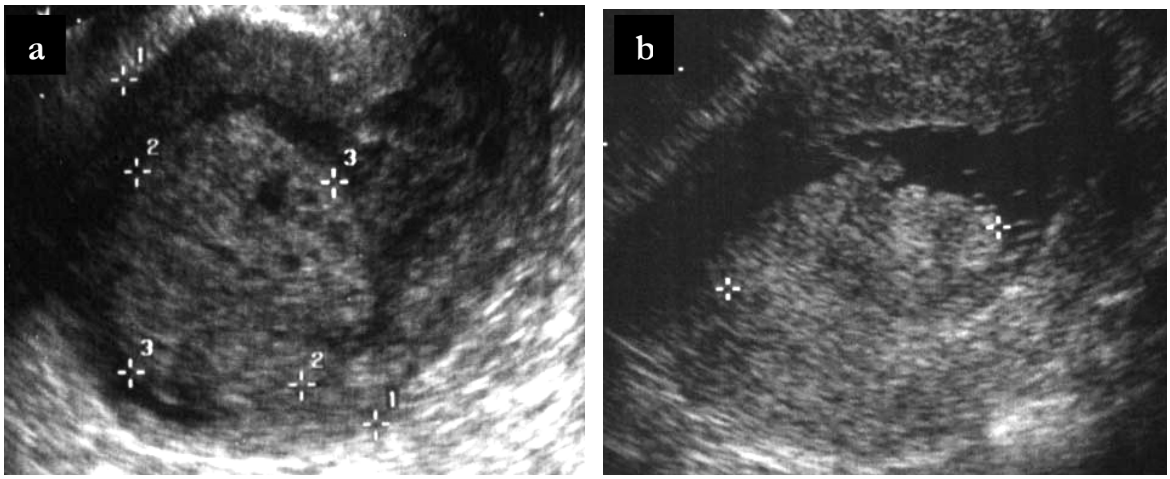


Figure 3. (a) endometrial cancer at conventional ultrasound; (b) endometrial cancer at hydrosonography

An *endometrial polyp* was suggested if the endometrium had a fairly homogenous echogenicity with or without cystic spaces, and if a hyperechoic line surrounded the central endometrial complex. At hydrosonography, a polyp was suspected if a smoothly-margined, hyperechoic focal lesion with or without cystic spaces protruded into the uterine cavity (Figure 4).

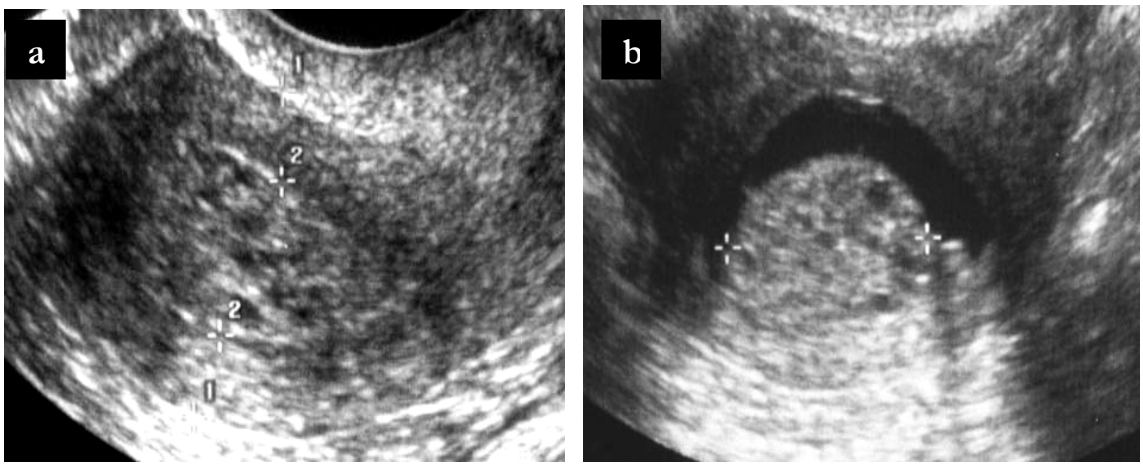


Figure 4. (a) polyp at conventional ultrasound; (b) polyp at hydrosonography

A *submucous myoma* was suggested at conventional ultrasound examination if a

submucosal mass continuous with the myometrium, and having echogenicity similar to the myometrium, bulged into the endometrium. At hydrosonography, a submucous myoma was suspected if a smoothly margined lesion connecting to the myometrium, and having echogenicity similar to that of the myometrium, protruded into the uterine cavity (Figure 5).

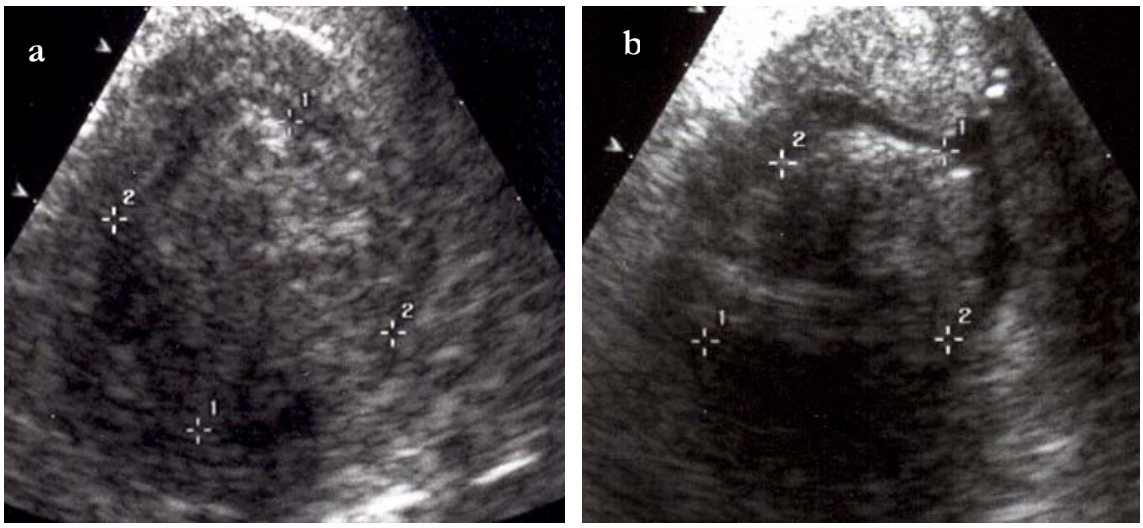


Figure 5. (a) submucous myoma at conventional ultrasound; (b) submucous myoma at hydrosonography

Power Doppler examination and computer analysis

All power Doppler ultrasound examinations were carried out using predetermined, standardised settings (Study V). To detect the most vasularized area of the endometrium, the entire endometrium was scanned with power Doppler ultrasound in the sagittal plane from one side to the other. The image of the most vascularized area of the endometrium (as estimated subjectively) was frozen, and the endometrium was outlined with callipers, using the trace function of the ultrasound system. The image was then post-processed, i.e., the grey scale echoes were removed so that the coloured power Doppler pixels were shown on a black background (Figure 6). In addition, the colour content of the most vascularized

area of the endometrium was rated subjectively by the examiner on a visual analogue scale of 0 to 100 arbitrary units (endometrial colour score). This subjective evaluation also took into account the colour hue of the power Doppler signals.

Analysis of the frozen images of the most vasularized area of the endometrium was done off-line (Study V). The images were transferred from the videotapes to a computer using a QuickCapture frame grabber (Data Translation, Marlboro, MA, USA). Analysis of the pixels in the ultrasound image was carried out using the NIH-Image Software, version 1.55 (National Institutes of Health, Bethesda, Maryland, USA). This software transforms colour pixels into grey scale pixels and allows analysis of 8-bit images in 256 grey scale levels. During computer analysis the outline of the endometrium was retraced manually. The area of the endometrium, and the mean intensity of pixels in the endometrium (MIEIUM), was calculated. The vascularized area was defined by filtering out pixels with an arbritary intensity of less than 25 units. The mean intensity of the pixels in the vascularized area (MIVA) was calculated. The percentage area of the endometrium that was vascularized was expressed as the vascularity index (the vascularized area divided by the area of the endometrium).

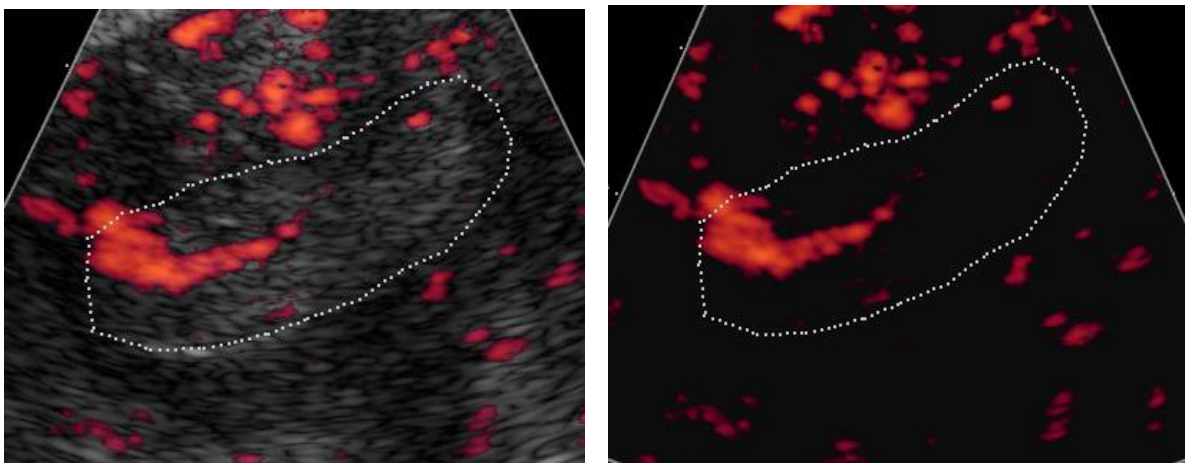


Figure 6. Images of the most vascularized area of the endometrium; (a) grey scale and power Doppler image, where the endometrial area is traced manually; (b) grey scale echoes removed by post processing, leaving the power Doppler pixels on a black background.

Diagnostic hysteroscopy

Diagnostic hysteroscopy was used as 'golden standard' to evaluate the presence of focally-growing lesions in the uterine cavity (Study IV). In addition, the ability of hysteroscopy to make a specific diagnosis was compared to that of conventional ultrasound and hydrosonography (Study IV). At hysteroscopy, intra-cavitary lesions were classified using predetermined criteria (Study IV): a malignant lesion was suggested if a vegetative, hypervascularized, and generally hard lesion was detected (Figure 7); a polyp was suspected if a smooth, poorly vascularized, soft, pedunculated lesion protruded into the cavity (Figure 8); a diagnosis of submucous myoma was made if a smooth, regularly-shaped or lobulated lesion distorted the contours of the uterine cavity (Figure 9).

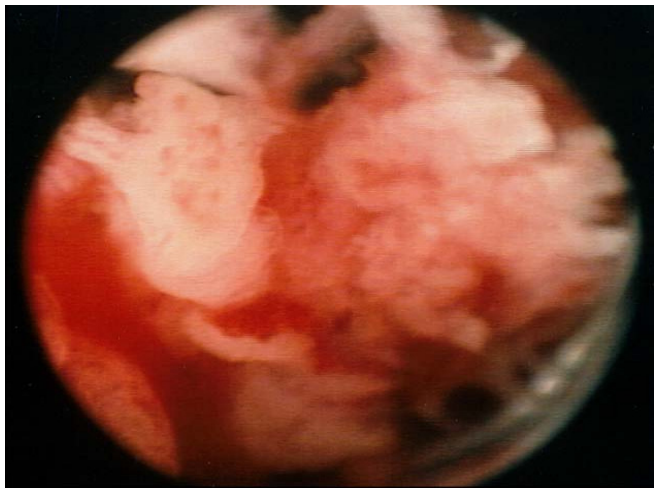


Figure 7. Endometrial cancer at hysteroscopy

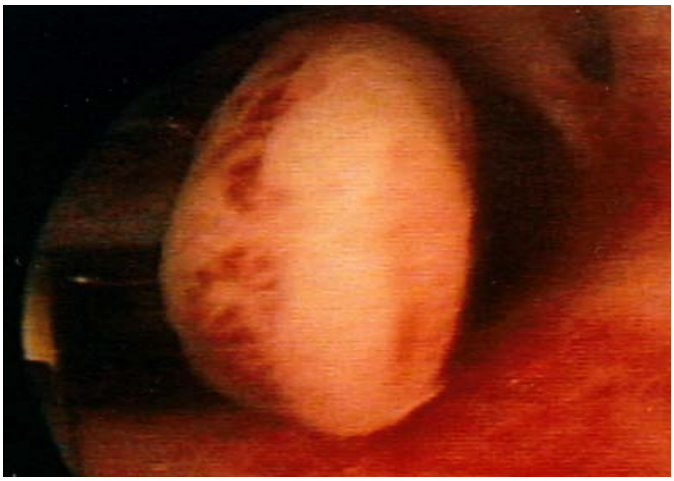


Figure 8. Endometrial polyp at hysteroscopy

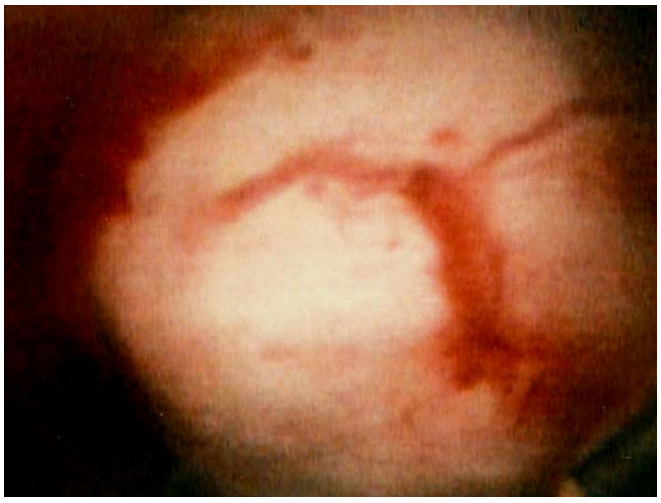


Figure 9. Submucous myoma at hysteroscopy

Endometrial biopsy techniques

Endorette[7]

Outpatient endometrial biopsies in Studies I and II were performed with the Endorette[7] sampling device. It was introduced into the endometrial cavity through the cervical canal, and advanced to the uterine fundus. The piston was retracted briskly to the full length of the sheath. Then the instrument was rotated, moved up and down, and withdrawn.

D&C

D&C was carried out under general anaesthesia in all women. Before cervical dilatation, endocervical curettage was performed. Curettage of the uterine cavity was then proceeded in a systematic fashion, beginning with the curette placed at the uterine fundus and applying even pressure on the endometrial surface. The curette was withdrawn the entire length of the uterus to the internal cervical os, and moved systematically around the whole uterine cavity. Finally forceps were introduced into the uterine cavity to grasp polyps or other focal lesions.

Hysteroscopic resection

All diagnostic and operative hysteroscopies in Studies III–V were performed under general anaesthesia by the gynaecological surgeon of the team within six weeks of the ultrasound examination. Hysteroscopy was carried out using a Storz resectoscope (10 mm) (Karl Storz, Tuttingen, Germany). The uterine cavity was expanded by infusion of glycine ethanol, the infusion pressure being 100 mmHg. Glycine ethanol was continuously infused while performing the resection. Focal lesions were removed, or a biopsy taken if the lesion was considered unresectable.

Moreover, biopsies were taken from the endometrium if the curettage specimen was scant.

Technique for overcoming cervical stenosis

In women with cervical stenosis, we tried to overcome the stenosis by grasping the cervix with a tenaculum, thereby deflexing the uterus, and inserting a minute uterine sound into the cervical canal to dilate the internal cervical os.

Histopathological analysis

All specimens collected at Endorette[7] sampling, D&C, or hysteroscopic resection were placed in a container of 10% formaldehyde and sent to the Pathology Department, at the University Hospital in Malmö, for processing and staining. The specimens from Studies II–V were analysed by the pathologist of the team (LS), and the specimens from Study I were analysed by different members of the Pathology department. A predetermined classification system for histological diagnosis was used (Table 2). In Study III–V, if the diagnosis differed among the specimens, the most relevant diagnosis was considered the conclusive one. Premalignancy/ malignancy in any specimen was considered the conclusive diagnosis.

Table 2. Histological classification system for endometrial pathology

Insufficient material
Normal endometrium
Proliferative endometrium
Secretory endometrium
Mixed hormonally-induced changes
Atrophic endometrium
Benign pathological endometrium
Simple hyperplasia
Complex hyperplasia
Focal hyperplasia
Endometrial polyp
Myoma
Premalignancy/ Malignancy
Complex hyperplasia with atypia
Endometrial cancer
Adenosarcoma

Statistics

Differences between groups

To test the statistical significance of differences in continuous data, the t-test was used for normally distributed data and the Mann-Whitney test was used in non-normally distributed data. The Chi-square test or Fisher´s exact test was used for unpaired categorical data. The McNemar test was used for paired categorical data, and Stuart-Maxwell´s test was used to compare paired categorical data in nine field tables.

Receiver operator characteristic (ROC) curves

ROC curves were drawn for continuous variables to determine the cut-off value that best discriminated between normal and pathological endometrium, or between benign and malignant endometrium. The best cut-off was defined as the point on the curve most distant from the reference line. The area under the ROC curve and the 95% CI of this area were determined. If the lower limit of the CI for the area under the ROC curve was above 0.5, the variable was considered to have a discriminatory potential. The statistical significance of differences in areas under the ROC curve was compared using a customised computer program, as described by Hanley and McNeil (Hanley 1983).

Multivariate logistic regression analysis

In Study V, multivariate logistic regression analysis was performed by backward stepwise selection of variables, using the likelihood ratio test to determine which variables to include in the model ($p < 0.05$ was taken as the threshold for inclusion). The probability of each patient having malignant endometrium was

derived from the regression equations. In a range from 0 to 1, a probability score close to 1 indicates a high risk of malignancy. ROC curves were drawn to determine the cut-off value of the calculated probability that best discriminated between benign and malignant endometrium.

Calculation of Risk

Odds ratio (OR) was used as an approximation of relative risk. An OR approximates how much more likely or unlikely the outcome will be for those with a variable present, than among those with it absent. An OR > 1.0 indicates a risk exceeding that of controls. The OR, with its 95% CI, was calculated by cross-tabulation.

Agreement between groups

Cohen´s Kappa (Cohen 1960) was used to assess agreement, with Kappa values of 0.81-1.0 indicating excellent agreement, 0.61-0.80 good agreement, and 0.41-0.60 moderate agreement (Brennan and Silman 1992).

Reproducibility of endometrial thickness measurements

Each observer took three replicate measurements of the endometrial thickness, unaware of her own results or those of the other observer. Intra-observer reproducbility was expressed as the difference between the highest and lowest value obtained by one observer, and as the *intra*-class correlation coefficient (Intra-CC). Inter-observer reproducibility was expressed as the difference between the mean of the three measurements taken by each observer, limits of agreement, and *inter*-class correlation coefficient (Inter-CC). Values for Intra-CC and Inter-CC above 0.75 are said to be acceptable (Burdock 1963). The limits of agreement define the range within which 95% of the differences between two observers are likely to fall. To

determine how precise our estimates of the limits of agreement were, we calculated the 95% CI of the lower and upper limits of agreement (Bland 1986). Bias between observers was assessed by calculating the 95% CI for the mean difference between the two observers. If zero lay inside this interval, no bias was assumed to exist.

General statistics

Statistical analyses were carried out using the Statistical Package for the Social Sciences software (SPSS Inc., Chicago, USA, 1996), Statview SE+Graphics™ software (Abacus Concepts, Inc., Berkeley, California, USA, 1988), and the StatXact-3 statistical program (Cytel Software Corporation, Cambridge, Massachusetts, USA, 1995). Calculations for Stuart Maxwell´s test were made manually. Exact confidence intervals (95% CI) were calculated using the binomial distribution, except when calculating the CI of the OR. Two-tailed p-values < 0.05 were considered statistically significant.

SONOGRAPHIC APPENDIX

Endometrial malignancy: power Doppler

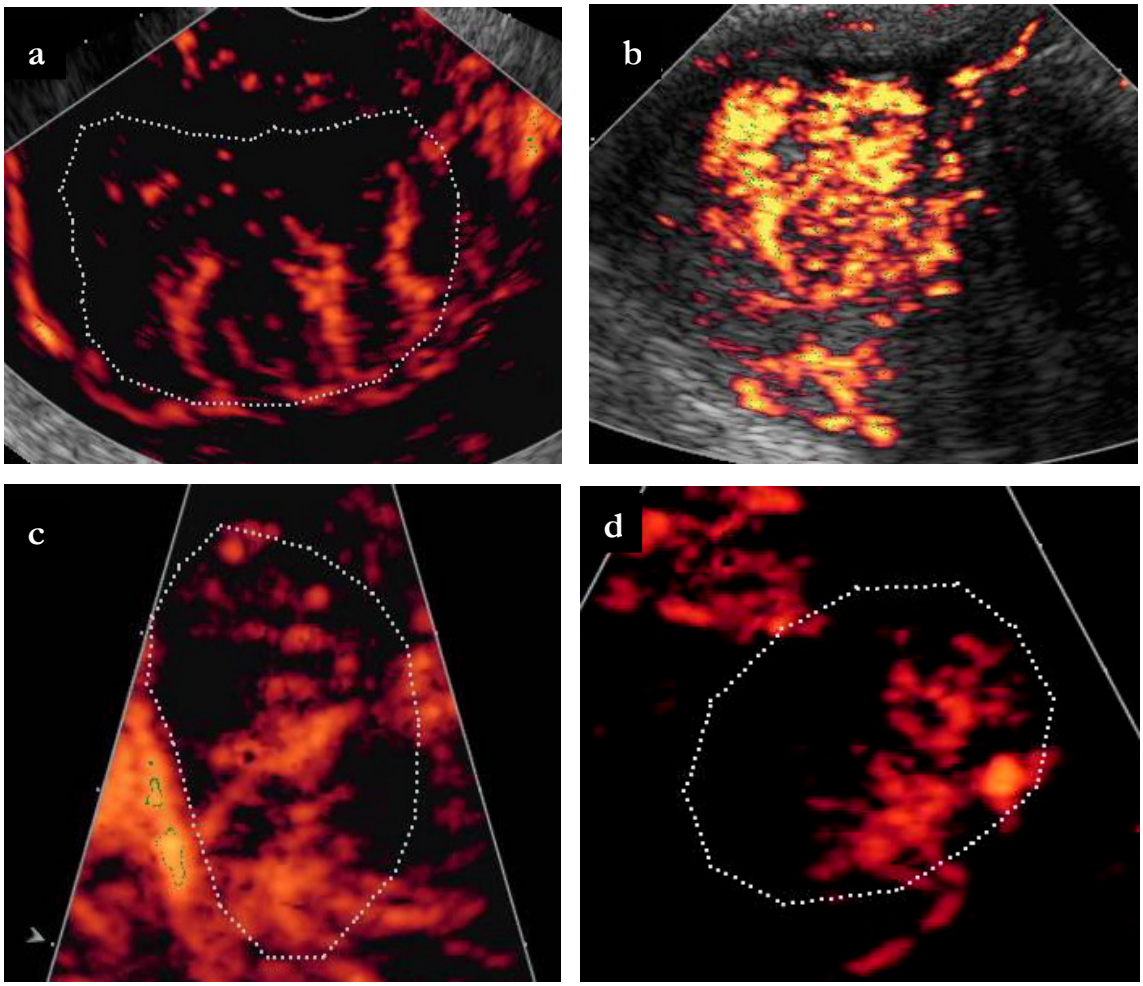


Figure 10. (a) adenosarcoma; (b-d) adenocarcinoma. Note; bizzare vessel-pattern.

Endometrial polyps: power Doppler

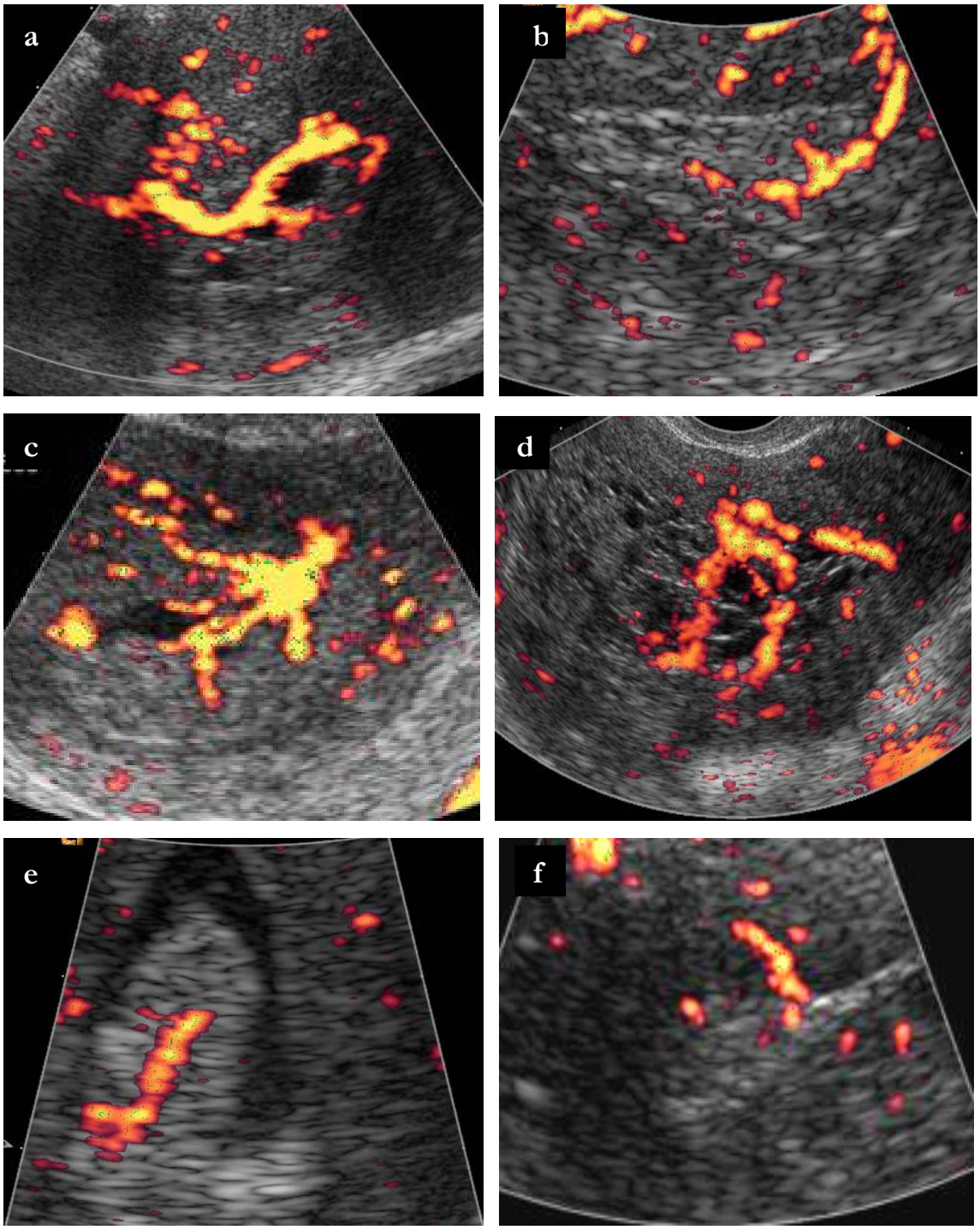


Figure 11. (a-f) endometrial polyps with feeding vessel(s). Note uncommon vessel-pattern; multiple branching in (c), multiple feeding vessels in (d).

Endometrial polyps: conventional ultrasound, hydrosonography

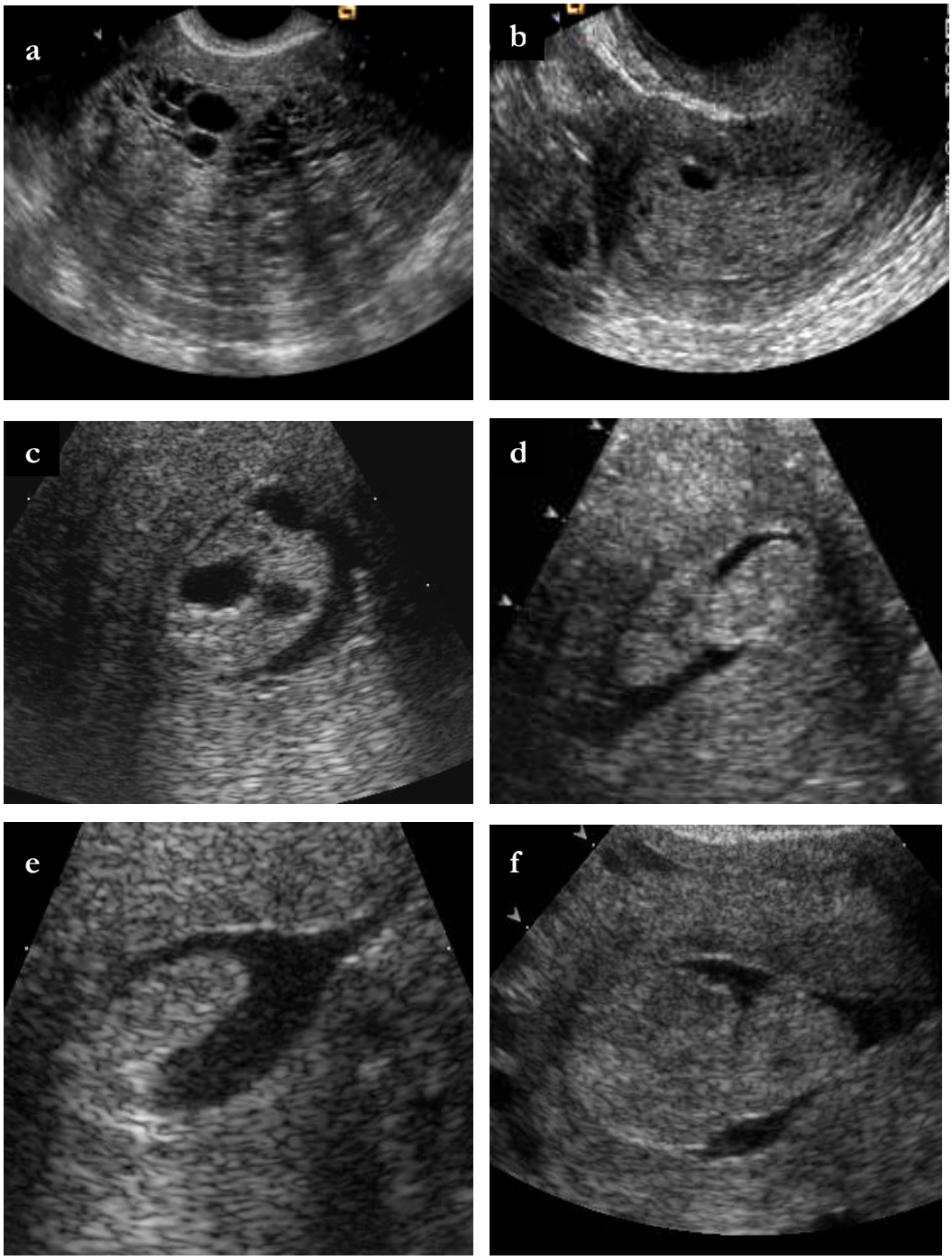


Figure 12. (a-f) endometrial polyps. Note; atypical appearance of (a+f).

Endometrial malignancy: hydrosonography

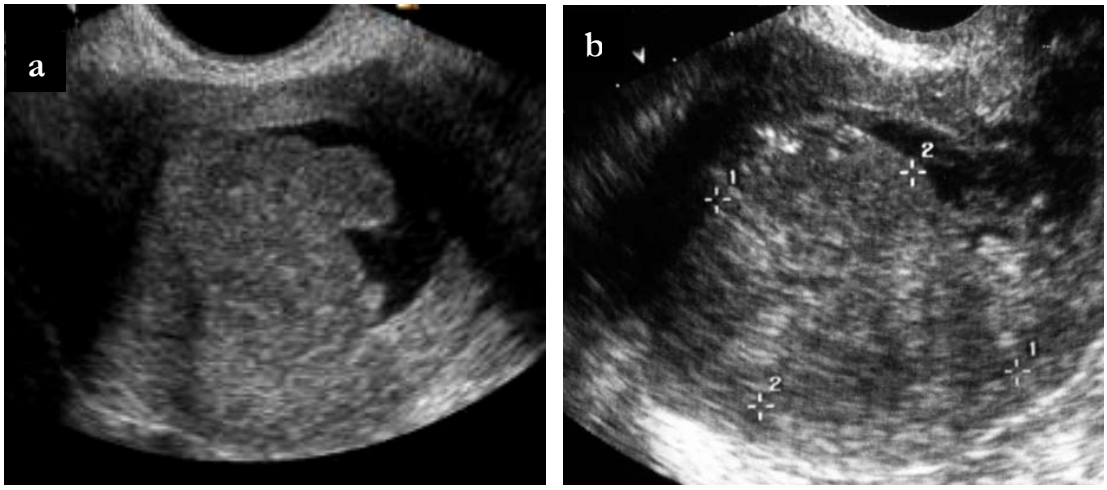


Figure 13. (a) adenocarcinoma; (b) adenosarcoma. Note; distension difficulties in (b).

Endometrial hyperplasia: hydrosonography

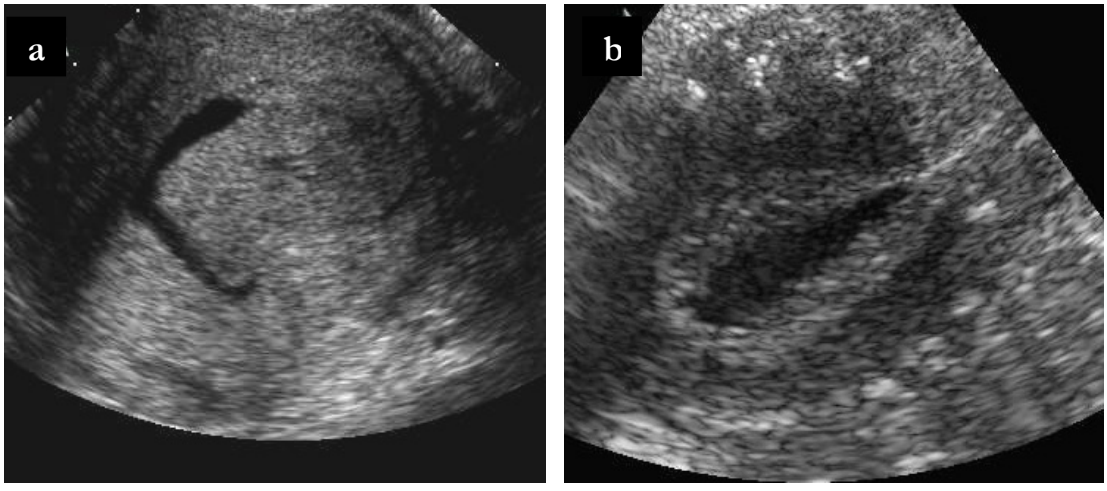


Figure 14. (a) focal hyperplasia; (b) complex hyperplasia.

DESIGN AND RESULTS

Study I

Re-bleeding and endometrial growth in women with post-menopausal bleeding and endometrium < 5 mm managed by D&C or ultrasound follow-up: a randomised controlled study

Design: Consecutive women presenting at the clinic with PMB and endometrium < 5 mm were randomised to ultrasound follow-up after 3, 6, and 12 months (n = 48) or to primary D&C with ultrasound follow-up at 12 months (n = 49). At all follow-up examinations, the endometrium was measured and the women were asked about re-bleeding. The endometrium was sampled at the 12 month examination in cases where sampling had not been performed previously because of re-bleeding or endometrial growth.

Results: Re-bleeding was reported by 33% (16/48) of the women in the ultrasound group and by 21% (10/48) of those in the D&C group (p = 0.12). Endometrial growth to $5 mm was found in 21% (10/48) of the women in the ultrasound group and in 10% (5/48) of those in the D&C group (p = 0.16). No endometrial pathology was found in women with isolated re-bleeding. Endometrial pathology during follow-up was found more often in women with endometrial growth than in those without (33% vs. 4%, p = 0.008) (Table 3). One endometrial cancer was found at the primary D&C, but no endometrial cancer developed during the follow-up year, or was found when searching the medical records and the regional cancer register 2.5 to 5 years after inclusion. Three women were found to have cervical carcinoma over the entire follow-up period.

Table 3. Complications within 12 months of a PMB, and endometrial pathology found at endometrial sampling during the 12 month follow-up period

	Ultrasound group (n = 48)		**D&C group (n = 48*)**	
	% (n)	Endometrial pathology	% (n)	Endometrial pathology
Complications				
Re-bleeding only	25 (12/48)	none	19 (9/48)	none
Re-bleeding and endometrium ≥ 5 mm	8 (4/48)	hyperplasia (n = 2)	2 (1/48)	none
Endometrium ≥ 5 mm, no re-bleeding	13 (6/48)	polyp (n = 1)	8 (4/48)	hyperplasia (n = 1)
No complications	54 (26/48)	complex hyperplasia** (n = 1)	69 (34/48)	hyperplasia (n = 1)

*One patient missing: primary D&C showed complex atypical hyperplasia; endometrial cancer shown in subsequent hysterectomy
**D&C performed because of pathological Pap-smear

Study II

Comparison of Endorette[7] and D&C for sampling of the endometrium in women with post-menopausal bleeding

Design: In a prospective study, 133 consecutive post-menopausal women presenting at the clinic with bleeding were examined by means of transvaginal ultrasound. After measuring the endometrial thickness, Endorette[7] sampling was performed without anaesthesia. D&C was carried out under general anaesthesia within six weeks. After completion of each sampling procedure, the women filled out a questionnaire regarding how they felt during the sampling.

Results: Endorette[7] sampling failed in 16% (21/133) of the women. The number of failed Endorette[7] biopsies was slightly higher (n = 13, 20%) among the first 66 as compared to the following 67 women (n = 8, 12%), even though the difference was not statistically significant (p = 0.22). More than half of the women (56%) experienced moderate or strong pain during Endorette[7] sampling, and the doctor underestimated the pain in 62% of the women. Endorette[7] failed to diagnose two of seven endometrial cancers found at D&C (29%; 95% CI 4%–71% using a normal approximation of the binomial distribution). In one of these two cases, the examiner suspected that the Endorette[7] device had not reached the uterine fundus. In women with endometrium < 7 mm, Endorette[7] and D&C showed similar results in obtaining an adequate endometrial sample and distinguishing normal endometrium from benign pathological endometrium and malignancy. In women with endometrium ≥ 7 mm, Endorette[7] yielded inadequate samples significantly more often than D&C (23% vs. 6%, p = 0.02, the McNemar test, Table 4), and missed all polyps and most hyperplasias (77%) diagnosed by D&C (Table 5).

Table 4. Agreement between Endorette® and D&C in yielding an adequate endometrial sample

	D&C		
Endorette®	Adequate	Inadequate	
Endometrium < 7 mm (n = 48)			
Adequate	20	12	
Inadequate	9	7	p = 0.66
Endometrium ≥ 7 mm (n = 51)			
Adequate	39	1	
Inadequate	9	2	p = 0.02

Note: The endometrium was unmeasurable in 9 women. The McNemar test was used

Table 5. Agreement in histological diagnoses between endometrial samples obtained with Endorette® and D&C

	D&C			
Endorette®	Normal endometrium	Benign pathology	Malignancy	
Endometrium < 7 mm (n = 48)				
Normal endometrium	42	1*	1	p = 0.61
Benign pathology	0	1**	0	Kappa = 0.64
Malignancy	1	0	2	Agreement = 0.94
Endometrium ≥ 7 mm (n = 51)				
Normal endometrium	24	19§	1	p < 0.001
Benign pathology	0	3§§	0	Kappa = 0.30
Malignancy	0	0	4	Agreement = 0.61

Pathological diagnosis according to D&C: *simple hyperplasia,**focal hyperplasia
§polyp (n = 13), focal hyperplasia (n = 4), simple hyperplasia (n = 2)
§§simple hyperplasia (n = 2), polyp (n = 1; the diagnosis in the Endorette® sample was simple hyperplasia)

Study III

Dilatation and curettage fails to detect most focal lesions in the uterine cavity in women with post-menopausal bleeding

Design: In a prospective study, 105 women with PMB and endometrium ≥ 5 mm underwent first diagnostic hysteroscopy, then D&C, and finally hysteroscopic resection of any focally-growing lesion still left in the uterine cavity after D&C. If the histological diagnosis differed among specimens from the same patient, the most relevant diagnosis was considered the conclusive one.

Results: Eighty percent (84/105) of the women in the study had pathology in the uterine cavity, and 98% (82/84) of the pathological lesions manifested a focal growth pattern at hysteroscopy. In 87% of the women with focal lesions in the uterine cavity, the whole or parts of the lesion remained *in situ* after D&C. D&C failed to diagnose 58% (25/43) of polyps, 50% (5/10) of hyperplasias, 60% (3/5) of complex atypical hyperplasias, and 11% (2/19) of endometrial cancers (Table 6). However, the agreement between the D&C diagnosis and the conclusive diagnosis was excellent (94%) in women without focally-growing lesions at hysteroscopy (Table 7). The percentage of removed polyps was related to the location of the polyp: isthmus, 0%; front/back wall, 80%; lateral walls, 20%; fundus, 27%. However, there was no significant difference in size or endometrial thickness between polyps that were removed by D&C and polyps that remained *in situ*.

Table 6. Agreement between D&C diagnosis and conclusive histological diagnosis

	Conclusive diagnosis								
D&C diagnosis	Insuff. sample	Normal endom.	Endom. Cancer	Adeno-sarcoma	CAH*	Hyperpl.**	Polyp	Myoma	**Total**
Insufficient sample	**4**	11	1	1		1	10	2	30
Normal endom.		**6**			1	4	12	2	25
Endom. cancer			**17**						17
Adenosarcoma									
CAH*					**2**				2
Hyperplasia**			1		2	**5**	3	2	13
Polyp							**18**		18
Myoma								**0**	0
Total	4	17	19	1	5	10	43	6	**105**

*Complex atypical hyperplasia
**Including simple hyperplasia, focal hyperplasia

Table 7. Agreement* between diagnosis based on D&C specimen and the conclusive diagnosis in relation to: presence or absence of focal lesions at hysteroscopy

	Conclusive diagnosis		
D&C diagnosis	Normal endom. or Insuff. sample	Benign Pathology	Premalignacy or Malignancy**
Focal lesion at hysteroscopy (n = 87)			
Normal endomerium or Insufficient sample	**5**	31	2
Benign pathology	0	**27**	3
Premalignancy or Malignancy**	0	0	**19**
No focal lesion at hysteroscopy (n = 18)			
Normal endometrium or Insufficient material	**16**	0	1
Benign pathology	0	**1**	0
Premalignancy or Malignancy**	0	0	**0**

*Agreement: focal lesion 0.59, no focal lesion 0.94
**Complex atypical hyperplasia, endometrial cancer, adenosarcoma

Study IV

Transvaginal sonography, hydrosonography, and hysteroscopy for the investigation of women with PMB and endometrium ≥ 5 mm

Design: In a prospective study, 105 women with PMB and endometrium ≥ 5 mm underwent conventional ultrasound examination and hydrosonography. Diagnostic and operative hysteroscopy under general anaesthesia was then performed. The presence of focally-growing lesions and the type of lesion (e.g., endometrial polyp, submucous myoma, or malignancy) was noted at ultrasound examination and at hysteroscopy. The ultrasound examiner and the hysteroscopist were unaware of each other=s findings when making their diagnoses. Hysteroscopic findings were used as the ›golden standard= with regard to detecting focally-growing lesions in the uterine cavity. The conclusive histological diagnosis of each woman was made on the basis of the most relevant diagnosis obtained by curettage, hysteroscopic resection, and hysterectomy, when performed.

Results: Hydrosonography was not performed in 6 women because of spontaneous fluid in the uterine cavity. It was successfully undertaken in 79% of the remaining women (78/99). In the first 53 women, 26% of the examinations failed and 40% were considered suboptimal; the corresponding figures for the following 52 examinations were 13% and 27% respectively. There was almost perfect agreement (96%) between hydrosonography and hysteroscopy in the diagnosis of focally-growing lesions, whereas conventional ultrasound missed 23% (15/65) of the focal lesions. Hydrosonography and hysteroscopy both correctly diagnosed approximately 80% of all endometrial polyps, whereas conventional ultrasound missed 50% of them (Table 8). Hysteroscopy was superior to both hydrosonography and conventional ultrasound with regard to discriminating

between benign and malignant lesions (Table 8). Two-thirds of the women with a poorly distensible uterine cavity had a malignant diagnosis. The risk of malignancy was increased sevenfold (OR 7.3, 95% CI 1.9–27.8) in women with distension difficulties at hydrosonography. Moreover, distension problems were more common among women with a malignancy of stage IC or more (i.e, invasion of the cancer into $\geq$ 50% of the myometrium) than among women with a malignancy of stage IB or less (5/7 vs. 2/17, i.e., 71% vs. 12%, p = 0.009; OR 18.8, 95% CI 2.1–170.2). Misdiagnosis of endometrial malignancy (false-positive/false-negative diagnosis) at hydrosonography was more common among women with suboptimal hydrosonography than among those with optimal hydrosonography (7/35 vs. 6/43, i.e., 23% vs. 14%; p = 0.55). However, if distension difficulties were added as a criterion for malignancy, the number of misdiagnoses were the same for suboptimal and optimal examinations (5/35 vs. 6/43, i.e., 14% vs. 14%).

Table 8. Efficacy of conventional ultrasound, hydrosonography and hysteroscopy in diagnosing polyps and uterine malignancy

	Polyp	**Malignancy**
Conventional ultrasound (n = 105)		
Sensitivity	0.49 (21/43)	0.60 (15/25)
False-positive rate	0.19 (12/62)	0.10 (8/80)
Hydrosonography (n = 78)		
Sensitivity	0.79 (26/33)	0.44 (7/16)
False-positive rate	0.24 (11/45)	0.06 (4/62)
Hysteroscopy (n = 105)		
Sensitivity	0.81 (35/43)	0.84 (21/25)
False-positive rate	0.06 (4/62)	0.15 (12/80)

Study V

An algorithm including results of grey scale and power Doppler ultrasound examination to predict endometrial malignancy in women with PMB

Design: Eighty-three women with PMB and endometrium ≥ 5 mm underwent grey scale and power Doppler ultrasound examination, using predetermined, standardised settings. Suspicion of endometrial malignancy at grey scale ultrasound examination (endometrial morphology) was noted, and the colour content of the endometrium at power Doppler examination was estimated subjectively (endometrial colour score). Computer analysis of the most vascularized area of the endometrium was done off-line, in a standardised manner. Stepwise multivariate logistic regression analysis was carried out to determine which subjective and objective ultrasound and power Doppler variables satisfied the criteria for their inclusion in a model used to calculate the probability of endometrial malignancy.

Results: Endometrial thickness, vascularity-index (vascularized area/endometrial area), and use of hormone replacement therapy (HRT) satisfied the criteria for inclusion in the equation $[e^z / (1+e^z)]$ to calculate the 'objective probability of malignancy', (where z = -3.543 + 0.078 x endometrial thickness (mm) + 0.066 x VI (%) - 3.357 x HRT use). Endometrial morphology, endometrial colour score, and HRT utilisation satisfied the criteria for their inclusion in the equation $[e^z / (1+e^z)]$ to calculate the 'subjective probability of malignancy', (where z = - 3.568 + 2.129 x endometrial morphology + 0.068 x endometrial color score (arbitrary units) -2.17 x HRT use). The ROC curves of the two multivariate logistic regression models and of the continuous individual variables that were included in the models are shown

in Figure 15. The values of the independent grey scale ultrasound and power Doppler variables, and of the regression models (calculating the probability of malignancy), were all significantly higher in malignant than in benign endometria (Table 9). At a fixed sensitivity of 0.88 (corresponding to the sensitivity at the optimal cut-off point for endometrial thickness), the specificity of 'the objective probability' of malignancy was superior to the specificity of all other ultrasound and power Doppler variables (p = 0.02 to 0.001). The 'objective probability of malignancy' detected more malignancies at endometrium 5–15 mm than endometrial morphology (p = 0.13) with similar specificity (Table 10).

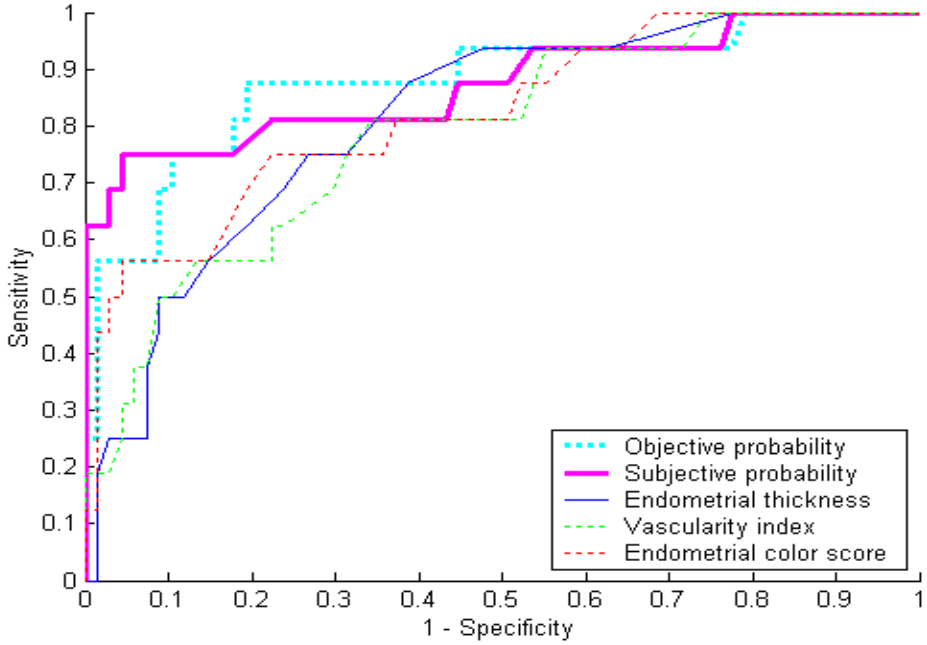


Figure 15. Receiver operator characteristic curves of 'objective and subjective probability' of malignancy and of variables included in the equations used to calculate the probability of malignancy

Table 9. Results of ultrasound examination in benign and malignant endometria

	Benign	**Malignant**	**P - value**
Endometrial thickness, mm; median (range)	9.0 (5 – 53)	18.0 (7 – 44)	< 0.001
Endometrial area, cm^2; median (range)	1.26 (0.16 – 15.0)	2.48 (1.1 – 22.2)	0.001
Vascularized area, cm^2 ; median (range)	0.1 (0 – 8.6)	0.9 (0.01 – 6.9)	< 0.001
Endometrial color score; mean ± SD	16.4 ± 14.4	44.9 ± 26.7	< 0.001
MIEIUM*; mean ± SD	21.3 ± 6.8	30.3 ± 10.7	< 0.001
MIVA**; mean ± SD	51.9 ± 16.2	60.7 ± 10.1	0.040
Vascularity index; mean ± SD	14.0 ± 13.0	31.5 ± 18.5	< 0.001
Subjective probability§; median (range)	0.06 (0.003 – 0.55)	0.71 (0.01 – 0.99)	< 0.001
Objective probability§§; median (range)	0.06 (0.001 – 0.74)	0.56 (0.007 – 0.96)	< 0.001

*MIEIUM = mean intensity of pixels in the endometrium
**MIVA = mean intensity of pixels in the vascularized area
§Calculated on the basis of endometrial morphology, endometrial color score, HRT use
§§Calculated on the basis of endometrial thickness, vascularity index, HRT use

Table 10. Sensitivity and specificity with regard to endometrial malignancy of endometrial morphology, and of 'subjective and objective probability of malignancy' at endometrial thickness ≤ 15 mm and > 15 mm

	≤ 15 mm		**> 15 mm**	
	Sensitivity	Specificity	Sensitivity	Specificity
Endometrial morphology	0.14 (1/7)	0.89 (51/57)	1.0 (9/9)	0.80 (8/10)
'Subjective probability of malignancy'	0.43 (3/7)	1.00 (57/57)	1.0 (9/9)	0.70 (7/10)
'Objective probability of malignancy'	0.71 (5/7)	0.86 (49/57)	1.0 (9/9)	0.50 (5/10)

Note: None of the differences were statistically significant (≤ 0.13 P ≤ 1.0; McNemar´s test)
The optimal cut-off for the 'subjective and objective probability of malignancy' was used (i.e., 0.32 and 0.21)

Study VI

Reproducibility of endometrial measurements in post-menopausal women

Design. Fifty-three post-menopausal women underwent transvaginal ultrasound examination by two sonographers. Each observer took three replicate measurements of the endometrium in each woman. Data were analysed for all women, as well as separately for women with endometrium ≤ 6 mm and > 6 mm. The agreement between observers in classifying women as having endometrium ≤ 4.4 mm or ≥ 4.5 mm was determined by calculating Cohen´s Kappa.

Results: The intra-observer reproducibility is shown separately for women with endometrium ≤ 6 mm and > 6 mm (Table 11). For the first observer, 82% (40/49) of the differences between measurements were ≤ 1 mm, and for the second observer, 67% (33/49) of the differences between measurements were ≤ 1 mm. The inter-observer reproducibility is shown separately for women with endometrium ≤ 6 mm and > 6 mm (Table 12). There was no systematic bias between the two observers, nor did the differences between the two observers vary in any systematic way over the range of values measured. In women with endometrium ≤ 6 mm the difference in endometrial thickness as determined by two observers was ≤ 1 mm in 71% (15/ 21) of the women vs. in 57% (16/28) of those with endometrium > 6 mm. According to the limits of agreement, 95% of the differences between two observers are likely to fall within ± 2 mm in women with endometrium ≤ 6 mm (Table 12). The mean difference between observers in women with endometrium ≤ 6 mm and no fluid in the cavity was 0.1 mm, compared to 0.5 mm in women with fluid in the cavity (fluid was included in the

measurements). The agreement between observers in classifying women as having endometrium ≤ 4.4 mm or ≥ 4.5 mm was excellent (Kappa 0.81), with only 4 discrepant cases.

Table 11. Intra-observer reproducibility of endometrial thickness measurements

	Endometrium, mm		Intra-CC*	Difference between highest and lowest measurement value, mm			
Endometrial thickness, mm	Median	Range		Median	10th percentile	90th percentile	Range
Observer 1							
≤ 6 mm (n = 22)	4.3	1.7 – 5.6	0.954	0.4	0.1	1.1	0.0 – 1.4
> 6 mm (n = 27)	9.1	6.1 – 65.6	0.997	0.7	0.2	2.3	0.0 – 2.9
Observer 2							
≤ 6 mm (n = 22)	3.8	0.8 – 5.9	0.879	0.7	0.1	1.9	0.1 – 2.2
> 6 mm (n = 27)	8.6	6.3 – 53.3	0.996	1.0	0.4	2.1	0.2 – 3.4

Note: median and range calculated from one value per woman (the mean of three measurements)
*Intra-class correlation coefficient

Table 12. Inter-observer reproducibility of endometrial thickness measurements

Endometrium, mm		Inter-CC*	Difference between the two observers, mm						
Median	Range		Mean	95% CI of mean	Lower limit	Upper limit	95% CI of lower limit	95% CI of upper limit	Range
≤ 6 mm (n = 21)									
3.9	1.8 – 5.5	0.77	0.23	-0.2 – 0.7	-1.6	2.1	-2.3 – (- 0.9)	1.3 – 2.8	-1.4 – 1.9
> 6 mm (n = 28)									
8.7	6.1 – 59.4	0.97	0.67	-0.4 – 1.7	-4.8	6.2	-6.7 – (-3.0)	4.3 – 8.0	-3.3 – 12.3

Note: Mean, median, and range calculated from one value per woman, i.e., the mean of six measurements
*Inter-class correlation coefficient

DISCUSSION

The aim of this thesis was to investigate the role of ultrasound in the management of women with PMB, with the intention of establishing the optimal treatment regime for every woman. The ability of ultrasound to select women for different biopsy methods was elucidated, and the performance of biopsy procedures in relation to sonographic findings was ascertained. It was investigated whether endometrial biopsy could safely be dispensed in subgroups of women with PMB. The usefulness of grey scale and power Doppler ultrasound in the risk estimation of endometrial malignancy were determined. Finally, the reproducibility of ultrasound measurements of endometrial thickness in post-menopausal women was examined.

Clinical implications

Ultrasound was found to be very useful in the management of PMB. Most of the important clinical questions raised were answered, but some still remain unresolved. Based on the results of this thesis, simple clinical guidelines can be set forth (see Clinical Guidelines). By using these guidelines, unnecessary invasive procedures can be avoided and, at the same time, the safety and accuracy of the investigation can be improved. The guidelines can assist individualising the timing and choice of endometrial biopsy procedures. Given appropriate training, all gynaecologists who counsel women with PMB can learn to measure the endometrial thickness accurately and to perform hydrosonography. In this way, they may select women at low-risk (endometrium < 5 mm) or high-risk (endometrium ≥ 5 mm) for endometrial pathology, and rule out focal lesions. However, measuring endometrial thickness is often difficult in post-menopausal women. In such cases, the patient should be referred to a specialised ultrasound

unit. It is important to emphasise that endometrial sampling should be considered mandatory in women where the endometrium cannot be measured because endometrial pathology, and even endometrial cancer, is not an uncommon finding in these women (Karlsson et al. 1995, Study II). Risk estimation of malignancy using endometrial morphology and power Doppler ultrasound should only be performed by experienced ultrasonographers using high quality equipment. In summary, the primary goal in the investigation of PMB is to select an optimal biopsy procedure. The secondary goal is to alert the practitioner to the possibility of estimating the risk of malignancy, thus enabling optimal timing of biopsy procedures, and even allowing the procedure to be confidently omitted in selected cases.

Measurement of endometrial thickness

Can we use the ≥ 5 mm cut-off both in women with and without HRT?

Smith-Bindman and co-workers (1998) did a meta-analysis of 35 studies comprising 5,892 women with PMB in order to determine the accuracy of transvaginal ultrasound in detecting endometrial abnormalities. Using a 5 mm cut-off to define abnormal endometrium, 96% of women with endometrial cancer and 92% of women with endometrial disease had an abnormal result, with a false positive rate (1-specificity) of 39% and 19%, respectively (Smith-Bindman et al. 1998). There was no significant difference in the sensitivity between HRT users and non-HRT users (Smith-Bindman et al. 1998). However, the number of women with a false positive result (i.e., women with endometrium > 5 mm and normal histological findings) was higher among women using HRT (23%), compared to women not using HRT (8%) (Smith-Bindman et al. 1998). The false positive rate possibly may be reduced by measuring the endometrial thickness within a week after the last progestin pill in women on sequential combined therapy. This is supported by the findings of Omodei and co-workers (2000), who showed that the endometrial thickness did not differ in women on sequential or continuous combined HRT (3.6 mm vs. 3.2 mm), if the measurement in question were taken on about the fifth day following the last progestin pill.

Conclusion: The ≥ 5 mm cut-off for defining pathological endometrium can be applied in all women, irrespective of HRT use, keeping in mind that there may be a higher false-positive rate among women on HRT.

Can we rely on endometrial thickness measurements ?

Measuring the endometrium in post-menopausal women is often more difficult

than in women of fertile age, due to the upright position of the uterus, the presence of vessel calcification, and a more diffusely marked endometrial myometrial border. In Study VI, most intra-observer differences in endometrial thickness measurements were small and the inter-observer reproducibility clinically acceptable; the agreement between observers in classifying women as having an endometrium < 5 mm or ≥ 5 mm was very good (Kappa 0.81).

It is striking how little has been written about the reproducibility of endometrial measurements in post-menopausal women with regard to the 5 mm cut-off point. Wolman and colleagues (1998), in a study on post-menopausal women, included only women with optimal measurement conditions (i.e., no uterine pathology—including fibroids, regular endometrium, and the endometrium capable of being visualized in its entirety). The mean difference in endometrial thickness measurements between observers was found to be 0.1 mm in women with endometrium 0–4 mm, and 0.3 mm in those with endometrium measuring 5–6 mm (Wolman et al. 1998). In our study, the corresponding figures were 0.3 mm and 0.2 mm. The results agree fairly well, despite the fact that we included all women with measurable endometrium.

Conclusion: The reproducibility of endometrial measurements, when taken by an experienced examiner using high quality ultrasound equipment and a standardised measurement technique, is clinically acceptable and allows reliable discrimination between those post-menopausal women with endometrium < 5 mm and those with endometrium ≥ 5 mm.

Management of women with PMB and endometrium < 5 mm

Is it safe to refrain from endometrial sampling in women with PMB and endometrium < 5 mm? If not, who should undergo sampling?

Unfortunately, there is no conclusive answer to these questions. In women with PMB and endometrium < 5 mm, no endometrial pathology was found in those with isolated re-bleeding during a 12 month follow-up, whereas endometrial pathology was common in women with endometrial growth. These results are in agreement with those of Gull and co-workers (2000), who managed women with PMB and endometrium < 5 mm expectantly by ultrasound follow-up at four and 12 months. In our study and in another by Gull and co-workers (2001), none of the 274 women with PMB and endometrium < 5 mm developed endometrial cancer when followed for up to five (Study I) or ten years. Based on these results, it would appear to be safe to manage women with PMB and endometrium < 5 mm expectantly with ultrasound follow-up, where only increased endometrial thickness to ≥ 5 mm should be an indication for sampling the endometrium. However, these conclusions are based on a relatively small number of women. Since none of the women we followed developed endometrial cancer during our study, the same being true of the women in the study by Gull and co-workers, we cannot be sure if endometrial growth is a better predictor of endometrial cancer than isolated re-bleeding.

Conclusion: If women with PMB and endometrium < 5 mm are to be managed expectantly with ultrasound follow-up, it seems justified, given the present state of our knowledge, to sample the endometrium—both in cases of re-bleeding and where there is endometrial growth to 5 mm or more. An appropriate time for ultrasound follow-up would be six months, because in our study most women with

endometrial growth had been identified by six months.

The cost-benefit of performing ultrasound follow-up on all women with PMB and endometrium < 5 mm can and probably will be questioned, especially in gynaecological departments/units with limited sonographic resources. Still, it is important to perform more studies on the management of women with PMB and endometrium < 5 mm to elucidate the optimal clinical strategy. In this way, in the future it should be possible to handle these women according to sound evidence, rather than 'qualified assumptions'. However, it might be as appropriate at the present to only tell women to return in case of re-bleeding. Otherwise the practitioner could routinely sample the endometrium at the time of a woman's first examination.

In the future, other factors might be taken into consideration when counselling women with endometrium approaching the cut-off point. Endometrial morphology might be one such factor. In a recently published study, Sheikh and co-workers (2000) found that that inhomogeneous endometrial appearance signified endometrial abnormality (including endometrial carcinoma) in women with PMB and endometrium < 6 mm. Perhaps ultrasound follow-up is unnecessary in women with a 'pencil line endometrium' (very thin, homogeneous endometrium with a regular border) measuring 1-2 mm. More studies exploring these issues are needed.

Be alert to the presence of cervical cancer, especially in women with PMB and endometrium < 5 mm!

Cancer of the cervix was diagnosed in three women during the entire follow-up period in Study I, making it an important differential diagnosis in women with

PMB and endometrium < 5 mm, as the risk of cervical cancer may be higher than that of endometrial cancer in these women. None of the three cervical cancers was suspected at clinical examination, and there was a one to two year delay in the diagnosis in two of these women because the attending physician either did not act on an abnormal pap smear, or the pap smear was false negative.

Conclusion: A pap smear should be mandatory in all women with PMB, and is particularly important in women with endometrium < 5 mm in cases where endometrial biopsy is not performed. In addition, colposcopy with directed biopsies from the cervix should be performed on liberal indications, such as ongoing bleeding. If re-bleeding occurs, a pap smear should be repeated because of its low sensitivity in diagnosing cervical cancer (Berek 1996).

Management of women with PMB and endometrium ≥ 5 mm

Fallacy that D&C removes and diagnoses focal lesions

In women with PMB and endometrium ≥ 5 mm, endometrial biopsy should be performed because endometrial pathology is common. The use of D&C as the 'golden standard' to obtain an endometrial biopsy in women with PMB may be questionable. According to the Nordic multi-center study, 60% of the women investigated had endometrial pathology (Karlsson et al. 1995), whereas in our study the figure was 80% (Study III). The discrepant results might be explained by our use of operative hysteroscopy (Study III), whereas Karlsson and colleagues (1995) used D&C as their 'golden standard'. It is easy to understand the impact the biopsy method has had on results, as D&C failed to diagnose 44% of the pathological lesions in Study III. This is in agreement with other studies comprising both pre- and post-menopausal women (Valle 1981, Stovall et al. 1989, Bettocchi et al. 2001). Focal growth of most pathological lesions (98%) might explain why they could not be removed by D&C (Study III). Not only did D&C fail to diagnose approximately half of the benign pathological lesions, but it missed 10% of the endometrial cancers as well (Study III). This is in agreement with the findings of Stovall (1989) and colleagues. In two studies on women with PMB and re-bleeding, who had an initially benign D&C, 23%–25% were found to have complex atypical hyperplasia or endometrial cancer within 5–10 years (Twu and Chen 2000, Gull 2001). These results indicate that some premalignant/malignant lesions were probably missed at the first D&C (Twu and Chen 2000, Gull 2001).

Focal lesions were completely removed by D&C in only 13% of the women (Study III). In studies on pre- and post-menopausal women, D&C was found to successfully empty the uterine cavity in 0%–62% of the women (Englund 1957,

Goldfarb 1989, Bettocchi et al. 2001, Gebauer et al. 2001). Differences in study populations, study design, and perhaps even the definition of 'empty cavity' might explain the heterogeneity of the results. In post-menopause, the majority of endometrial polyps have fibrotic transformation of the stroma (i.e., atrophic polyps), making them more difficult to remove by D&C (Reslova et al. 1999). Gerbauer and co-workers (2001) used two surgical teams, one doing hysteroscopy and one performing D&C, whereas in our study the same surgeon performed both procedures. In the latter case, there is the potential risk of conscious or unconscious operator bias. Nevertheless, the results of Study III and of other studies show that D&C frequently fails to diagnose benign pathology and sometimes endometrial cancer as well, commonly leaving parts of the lesions behind in the uterine cavity (Englund 1957, Valle 1981, Goldfarb 1989, Stovall et al. 1989, Bettocchi et al. 2001, Gebauer et al. 2001).

Conclusion: D&C is not accurate in making a correct diagnosis in women with focal lesions in the uterine cavity. Therefore, focal lesions need to be ruled out before D&C can be recommended. The use of D&C as the 'golden standard' when assessing other biopsy methods should be abandoned.

Is it necessary to remove 'polypoid lesions'?

In the first instance, one can never be sure of a benign polyp until the lesion has been completely removed since endometrial cancer is quite frequently confused with benign polyps, both at hysteroscopy and at hydrosonography (Study IV). Secondly, polyps may grow back if they are not properly removed (Bouda et al. 2000), causing re-bleeding and resulting in repeated diagnostic procedures. Bouda and co-workers (2000) found regrowth of polyps in 46% (46/100) of the women who had undergone D&C vs. in only 14 % (11/81) of those treated with operative

hysteroscopy. Regrowth of polyps were only seen if the polyp or the endometrium was proliferative or hyperplastic, whereas none of the atrophic polyps resulted in regrowth (Bouda et al. 2000). Thirdly, there are studies indicating that both polyps and hyperplasia are risk factors for developing endometrial cancer (Sherman and Brown 1979, Kurman et al. 1985, Pettersson et al. 1985). Finally, Anastasiadis and co-workers (2000) found pre-malignant changes in 24% (30/126) and malignant changes in 1.5% (2/126) of polyps extracted by D&C.

Conclusion: There is firm evidence supporting complete removal of all polypoid lesions in women with PMB.

Can ultrasound select those focal lesions that benefit most from operative hysteroscopy?

A large proportion of women with PMB may benefit from operative hysteroscopy because approximately 85% of the women we have studied with PMB and endometrium ≥ 5 mm had focally growing lesions. However, in many gynaecological departments, operative hysteroscopy is performed under general anaesthesia, making the procedure time-consuming and expensive (usually more so than D&C). Under these circumstances, there is a 'clinical' desire to limit the number of women referred for operative hysterocopy. The question is whether it is possible to use sonographic criteria to select those women who are most likely to benefit from operative hysteroscopy. We found that the location of the polyp, rather than its size, determined if it would be removed by D&C or not (Study III). On the other hand, Gebauer and colleagues concluded that the size of the lesion was of importance, since D&C failed to remove the majority of focal lesions if the endometrium measured ≥ 10 mm (Gebauer et al. 2001). An attractive alternative solution would be to perform more operative hysteroscopies under local

anaesthesia, using minimally invasive instruments. This could bring down the cost and shorten the interval from sonography to surgery.

Conclusion: Hysteroscopy might be especially beneficial in women with endometria measuring ≥ 10 mm whose focal lesions are not attached to the back or front walls of the uterine cavity at ultrasound examination. However, these findings have been based on a small number of women, limiting the generalisability of the results.

How should we sample the endometrium in women with PMB and endometrium ≥ 5 mm, but with no focal lesions?

If there is no focal lesion, should we perform D&C, or are simple endometrial sampling devices like Pipelle® or Endorette® adequate? Is the diagnostic performance dependent on endometrial thickness? To answer this question, the diagnostic accuracy of Pipelle®/Endorette® and D&C must be compared in women whose endometrium has been measured and where focal lesions have been excluded. Hysteroscopy/hysterectomy should be used as the 'golden standard'. To the best of my knowledge, no such study exists. We did compare Endorette® and D&C, but without knowing whether focal lesions were present in the uterine cavity (Study II). With the current state of knowledge, Study II should have included hydrosonography to exclude focal lesions and operative hysterocopy as 'golden standard'. In women with endometrial thickness < 7 mm, Endorette® and D&C had similar diagnostic properties, whereas Endorette® missed all polyps and more than half of hyperplasias in women with endometrium ≥ 7 mm (Study II). In addition, two of seven endometrial cancers were missed by Endorette®. In one of the two cases, the examiner was uncertain whether or not the sampling device had entered the uterine cavity. This emphasises the necessity of ensuring that the sampling device reaches the uterine fundus (either by measuring the cavity using

the sampling device, and not allowing sampling to proceed if the measurement of the uterine cavity is < 5 cm; or by ascertaining the correct placement of the device in the cavity by ultrasound). In contrast to our findings, the results of a recently published meta-analysis showed that Pipelle® (which is similar to Endorette®) was the most accurate outpatient sampling device. Pipelle® had a sensitivity of 99.6% and a specificity of 99.5% in diagnosing endometrial cancer; and a sensitivity of 82% and a specificity of 98% in diagnosing atypical hyperplasia in post-menopausal women (Dijkhuizen et al. 2000). There are, however, methodological shortcomings in this study, as pointed out by the authors themselves. They cite possible publication bias, only a minority of the studies (27%) had a true reference standard (hysterectomy), and a large proportion of the primary studies were of poor quality. A greater number of high quality studies are needed to determine if Pipelle®/Endorette® are reliable diagnostic tools in women without focal lesions at hydrosonography, since omitting D&C in these women could save money, inconvenience for the patient, and possibly morbidity.

Conclusion: Although based on inconclusive evidence, it is probably safe to use Endorette® in women with no focal lesions in cases where the endometrium measures < 7 mm, whereas D&C might be preferable in women with endometrium ≥ 7 mm. Another possible regime would be to use Endorette® or Pipelle® primarily on all women with no focal lesions, reserving D&C for women with insufficient, or failed, Endorette®/Pipelle® biopsy.

Does operator experience affect the success rate of endometrial sampling using Endorette® or Pipelle®?

There seems to be an association between operator experience and the efficacy of simple sampling devices. The number of failed Endorette® biopsies tended to

decrease as Study II progressed, while the proportion of inadequate samples did not change. Moreover, Gordon and Westgate (1999) found that inadequate and failed Pipelle® biopsies were significantly more common among inexperienced than experienced operators, and that these differences became very obvious in post-menopausal women.

Conclusion: Experienced operators will probably perform Pipelle®/Endorette® sampling more accurately than inexperienced ones.

The significance of an inadequate Endorette®/Pipelle® specimen

The significance of an inadequate Pipelle® biopsy is another important issue. The high sensitivity of Pipelle® in diagnosing endometrial cancer (Dijkhuizen et al. 2000) might mislead us into believing that an inadequate endometrial sample reflects the absence of endometrial disease. In Study II, 22% of the women with an inadequate Endorette® sample were found to have endometrial pathology at D&C (7/31: six polyps, one endometrial cancer). Farell and co-workers (1999) found that only two-thirds of the women with an inadequate Pipelle® specimen were referred for further diagnostic procedures (i.e., ultrasound or surgery). Among the women who subsequently underwent hysteroscopy or hysterectomy 37% had, uterine abnormalities (27/73: two endometrial cancers, two other uterine malignancies, three atypical hyperplasias, three simple hyperplasias, one myoma, 16 polyps) (Farrell et al. 1999). These figures would probably be much lower if ultrasound were used as the initial diagnostic tool in the investigation of all women with PMB, with only those women who then exhibited no focal lesions at ultrasound examination and endometrium < 7 mm being selected for Pipelle®/Endorette® sampling.

Conclusion: All operators should be made aware that an inadequate Pipelle®/Endorette® sample does not exclude endometrial pathology.

Can hydrosonography reliably detect focal lesions?

There was almost complete agreement (96%) between hydrosonography and hysteroscopy in diagnosing focally-growing lesions, whereas conventional ultrasound missed one-quarter of the focal lesions (Study IV). This is in agreement with other studies comprised of both pre- and post-menopausal women, the reported sensitivity of hydrosonography being 93%–100% and the false-positive rate 6%–15% when hysteroscopy or hysterectomy findings were used as the 'golden standard' (Widrich et al. 1996, Bernard et al. 1997, Williams and Marshburn 1998, Kamel et al. 2000). Hydrosonography has advantages over out-patient hysteroscopy. It is better tolerated by patients and less expensive (Widrich et al. 1996, Timmerman et al. 1998). Moreover, hydrosonography is easy to learn and can be performed quickly, with a minimum of extra equipment, as part of an ultrasound examination.

Conclusion: Hydrosonography can easily and reliably rule out focal lesions. It should preferably be performed on all women with PMB and endometrium $\geq$ 5 mm.

Methodological aspects—hydrosonography

Learning-curve

The failure rate and the number of suboptimal examinations decreased as Study IV progressed. Suboptimal or failed examinations due to cervical stenosis, poor visualisation of the cavity (due to air bubbles, uterine position, or myomas), and difficulties in getting access to the cervix, tended to be less common in the second part of the study. In the latter part of the study, these problems could often be avoided by using, for example, a minute uterine sound to get past cervical stenosis, flushing the catheter before insertion to avoid air bubbles, and managing difficult uterine positions by using the free hand.

What catheter should be employed for hydrosonography?

The first consideration when choosing a catheter is the material. Some use baby feeding catheters that are very soft and pliable, whereas we used one made of fairly rigid polyethylene (Kremer de la Fontaine). The advantage of using a more rigid catheter is that it is easier to insert through the cervix with minimal additional instrumentation.

Secondly, should a balloon or a non-balloon catheter be used? In Study IV, we preferred a catheter without an inflatable balloon because it was better tolerated by patients (Snyder and Anasti 2000) and also considerably less expensive than a balloon catheter. On the other hand, one must bear in mind that almost half of examinations in Study IV were considered suboptimal, and that backflow or distension problems were the cause of failure in two-thirds of those cases. Confusion of uterine malignancy and endometrial polyps tended to be more

common among women with suboptimal hydrosonography examinations—at least if distension difficulty was not added as a malignancy criterion (Study IV). Theoretically, the risk of spreading malignant cells when using a balloon catheter rather than a non-balloon one may be greater because of the higher intrauterine pressure created, even though the present writer has not been able to locate any randomised studies investigating what impact the choice of catheter may have on a patient's survival rate. Such a study would probably be difficult to perform, since death from endometrial cancer is quite uncommon in women with stage I of this disease, suggesting that a large patient population would have to be examined and followed for a long time. In addition, it may be unethical to use a balloon catheter in the investigation of PMB, as it has not been shown to be clinically superior to a non-balloon catheter

Conclusion: Use of a non-balloon catheter should suffice for ruling out focal lesions, which is the most important objective when performing hydrosonography.

Methodological aspects—hysteroscopy

Hysteroscopy–does it facilitate dissemination of malignant cells?

All women with endometrial malignancy in Study IV underwent hysteroscopy and hysteroscopic resection. Of the 25 women with endometrial carcinoma, only one with stage IIIA carcinoma had positive peritoneal cytology. Two recently published retrospective studies have shown that hysteroscopy prior to hysterectomy due to endometrial carcinoma might lead to dissemination of malignant cells into the abdomen from the uterine cavity (Obermair et al. 2000, Zerbe et al. 2000). However, in a retrospective study on women with endometrial carcinoma, stage IA or IB, there was no difference in the disease-free five year survival rate between women who had undergone hysteroscopy before laparotomy (n = 135) and those who had not (n = 127) (Obermair et al. 2001). Nor was there a higher prevalence of positive peritoneal cytology in the former group (Obermair et al. 2001). In addition, two other studies show that positive peritoneal cytology in the absence of other extrauterine disease or other poor prognostic factors probably has no significant effect on recurrence or survival (Lurain et al. 1991, Kedar et al. 1994).

Conclusion: There is no strong evidence that hysteroscopy has a negative effect on the prognosis of women with endometrial malignancy. Thus, operative hysteroscopy, and thereby also hydrosonography, can be presumed to be safe in the investigation of women with PMB until additional findings show otherwise.

Making a specific preoperative diagnosis based on sonographic findings

Can grey scale ultrasound reliably discriminate between polyps and endometrial cancer?

We know that certain sonographic characteristics are suggestive of endometrial polyps (e.g., cystic spaces within the endometrium) and endometrial cancer (e.g., inhomogeneous endometrial texture) (Kurjak et al. 1993, Sheth et al. 1993, Atri et al. 1994, Hulka et al. 1994). However, the findings in these studies indicate the existence of overlapping features between benign and malignant conditions, limiting the clinical usefulness of these findings. On the other hand, Weber and colleagues (1998) found that the accuracy of transvaginal sonography in detecting endometrial pathology increased if endometrial morphology (homogenous/inhomogenous) and endometrial border appearance (regular/irregular) were combined with endometrial thickness. The studies cited above correlated endometrial characteristics with histological diagnosis, whereas we prospectively tried to make a specific diagnosis based on predetermined sonographic criteria (Study IV). The ability of various diagnostic methods to make a specific diagnosis of endometrial polyps are shown in Table 13.

Table 13. Comparison of conventional ultrasound, hydrosonography, out-patient hysteroscopy, and hysteroscopy under general anaesthesia in the correct diagnosis of endometrial polyps

	Endometrial polyps	
	Sensitivity	Specificity
Conventional ultrasound		
Study IV	49%	81%
Other studies*	33%–56%	97%–100%
Hydrosonography		
Study IV	78%	76%
Other studies**	58%–91%	90%–100%
Out-patient hysteroscopy		
Widrich et al. 1996	94%	90%
Hysteroscopy under general anaesthesia		
Study IV	81%	94%
Schwarzler et al. 1998	92%	100%

Note: all studies below include both pre- and post-menopausal women
*Cicinelli et al. 1994, Schwarzler et al. 1998, Widrich et al. 1996
**Cicinelli et al. 1994, Bernard et al. 1997, Schwarzler et al.1998

The values for sensitivity in the studies cited agree fairly well with our results, but the specificity of conventional ultrasound examination and hydrosonography were lower in our study. The difference in results might be explained by the varying study populations and their divergent proportion of malignancies, i.e., 24% in Study IV vs. 0%–5% in the other studies in Table 13, (since endometrial malignancies are often confused with polyps, and vice versa) (Study IV). There are few other studies evaluating the ability of hydrosonography to discriminate between benign and malignant endometrial lesions. By defining all focal inhomogeneous lesions and all focal lesions ≥ 5 mm as "suspicious", Dubinsky and colleagues (1995) obtained a high sensitivity (8/9 = 89%), but also a low specificity (36/79 = 46%) in diagnosing endometrial malignancy at hydrosonography. Bernard

and co-workers (1997) reported a sensitivity of 40% (2/5) and a specificity of 100% with regard to malignancy. The latter findings are in agreement with our results, suggesting that a definition of a "suspicious lesion" similar to ours was used.

The outcome of our investigation suggests that the sonographic criteria for identifying polyps and uterine malignancies need to be redefined, since polyps and cancers are often confused with each other at hydrosonography. A study elucidating the association between sonographic characteristics and histological findings would be very valuable for the interpretation and understanding of endometrial morphology when examined by ultrasound.

Conclusion: Endometrial morphology at grey scale ultrasound (with or without saline infusion) cannot reliably discriminate between benign and malignant lesions.

Estimating the risk of malignancy—individual factors

Does the use of HRT lower the risk of endometrial cancer?

Smith-Bindman and colleagues (1998) found that a normal transvaginal scan, i.e., endometrium < 5 mm, reduced the risk of cancer about ten-fold, regardless of HRT use. Thus, in an unselected population of women with PMB, the risk of endometrial cancer will drop from 10% to 1% among women not using HRT, and from 1% to 0.1% in HRT users, following a normal transvaginal scan (Smith-Bindman et al. 1998). In Studies I-VI, the prevalence of endometrial carcinoma among women with PMB and endometrium ≥ 5 mm was 2% (1/55) among HRT users, and 23% (29/124) among non-HRT users; only one woman with endometrium < 5 mm had endometrial carcinoma (a woman using unopposed oestrogen therapy!) (Study I). In addition, HRT use was found to be the most powerful protective variable in the multivariate regression models calculating the risk of endometrial malignancy: HRT considerably lowered the risk of malignancy (Study V). These results may reflect the fact that PMB is more common among HRT users, and that the cause of bleeding in these women is more likely to be dysfunctional, rather than due to an organic abnormality. Another theory is that HRT use actually reduces the risk of endometrial cancer. Most women on HRT in our studies (74/105 = 70%) used continuous combined therapy (estradiol + noretisterone acetate). In fact, Weiderpass and co-workers (1999) showed that the use of continuous combined HRT for five years or more reduced the risk of endometrial carcinoma five-fold (OR = 0.2, 95% CI = 0.1–0.8 for 5 or more years of use), whereas sequential HRT tripled the risk (OR = 2.9, 95% CI = 1.8–4.6 for 5 or more years of use), as compared to non-HRT users during the same period of time. In the latter study the protective potential of continuous combined HRT was confined only to testosterone-derived progestins like noretisterone acetate

(Weiderpass et al. 1999). In addition, continuous combined HRT has been reported to normalise the endometrium in women with complex hyperplasia (Feeley and Wells 2001). Other studies have shown that using sequential combined HRT with progestins at least ten days per month, or continuous combined HRT, at the very least will not increase the risk of endometrial cancer (Pike et al. 1997, Archer 2001, Feeley and Wells 2001).

Conclusion: Since HRT use and the type of HRT taken are important factors in estimating the risk of endometrial cancer in women with PMB, such information should be included in the clinical decision-making. The higher likelihood of endometrial malignancy among non-HRT users should be kept in mind.

Are high BMI and diabetes risk factors for endometrial cancer?

Using a multivariate logistic regression model, Ferrazi and co-workers (1996) showed that age and body mass index (BMI) were independent variables associated with a significantly increased risk of endometrial cancer. Others have also found a positive association between BMI and endometrial cancer (Folsom et al. 1989, Jain et al. 2000, Weiderpass et al. 2000). Folsom and co-workers (1989); determined that the risk of endometrial cancer increased in relation to the amount—but not the distribution—of fat whereas Iemura and co-workers (2000) found that upper body fat distribution, rather than overall adiposity, correlated with endometrial cancer. In Study V, BMI was retrospectively added to our multivariate logistic regression analysis as an independent variable (height and weight data were found in the records of 63 of the 83 women). In our analysis, BMI did not satisfy the criteria for inclusion in the model. Whether or not diabetes has an impact on the risk of endometrial cancer remains controversial . Some case-control studies show that diabetes is an independent risk factor for endometrial cancer (Parazzini et al. 1999,

Weiderpass et al. 2000). Other have concluded that increased risk is present only in overweight diabetic women (Shoff and Newcomb 1998).

Conclusion: It may be advisable to consider BMI—and possibly diabetes as well—when constructing new models to calculate the risk of endometrial malignancy.

Do genetic factors influence the risk of endometrial cancer due to exogeneous estrogens?

Common variants among genes coded for enzymes in the sex steroid biosynthetic pathways may influence the risk of endometrial cancer. Haiman and co-workers (2001) found that women homozygous for the A2-allele of the CYP17 gene had a decreased risk of endometrial cancer (OR = 0.43, 95% CI, 0.23–0.80). McKean-Cowdin and co-workers (2001), however, found that women homozygous for the T-allele had an increased risk of endometrial cancer in combination with estrogen only-therapy (OR = 4.1, 95% CI, 1.6–10.3). This indicates that variants of the CYP17 gene may be potential markers of endometrial cancer susceptibility due to exogenous oestrogens. Unfortunately, the exact definition of estrogen replacement therapy was not stated in this study (McKean-Cowdin et al. 2001). Unopposed systematic estrogens are very seldom used today because of increased risk of endometrial cancer (Weiderpass et al. 1999). Still, we do not know if the findings by McKean-Cowdin and co-workers (2001) also apply to women using estriol or vaginally-administered estradiol (used by about 20% of those in our studies).

Conclusion: Although the clinical relevance of the CYP17 gene is still unproven, preliminary data suggests that CYP17 may be a marker of up-regulated estrogen biosynthesis and metabolism, and as such may be of utility in studies on endometrial cancer risk.

Estimating the risk of malignancy—sonographic features

Distension difficulties at hydrosonography–a new malignancy criterion

A poorly distensible uterine cavity at hydrosonography was significantly more common among women with a malignant, rather than a benign diagnosis. Such distension problems tended to be even more common in women with endometrial cancer which show deep myometrial invasion (Study IV). In agreement with our results, Lafier-Narin and co-workers (1999) found a poorly distensible uterine cavity in all of three patients with endometrial carcinoma (3/3). The same association was noted in another study comprising four malignancies (Bree et al. 2000).

Conclusion: Distension difficulties at hydrosonography should be regarded as a new malignancy criterion.

Can three-dimensional (3D) ultrasound contribute to the diagnosis of endometrial malignancy?

Gruboeck and co-workers (1996) found that the endometrial volume, as measured by means of 3D ultrasound, constituted a superior diagnostic test for the detection of endometrial cancer in women with PMB, than did measurement of endometrial thickness. Using the optimal cut-off value of 15 mm (according to the ROC-curve), they found that endometrial thickness had a sensitivity of 83% and a specificity of 88% in diagnosing endometrial cancer, whereas volume measurements had a sensitivity of 100% and a specificity of 99%, when employing a cut-off value of 13 ml. Of a total of 11 malignancies in this study, only three were invading less than half of the myometrium (i.e., stage IA or IB), and only two had an endometrial

thickness of less than 15 mm. Thus we do not know conclusively if 3D volume measurements can help to diagnose early/small endometrial malignancies. In a study comprising 36 women with PMB (including 3 endometrial cancers), Bonilla-Mussoles and co-workers (1997) concluded that 3D hydrosonography might be helpful in distinguishing benign from malignant lesions, and in determining myometrial invasion in women with endometrial cancer.

Conclusion: The clinical utility of 3D ultrasound in diagnosing endometrial cancer remains uncertain.

Can power Doppler contribute to diagnose endometrial malignancy?

We found that endometrial vascularity assessed by power Doppler contained diagnostic information that could help us to differentiate between benign and malignant endometrium (Study V). The greater the colour content of the endometrium (whether subjectively or objectively assessed), the greater the risk of endometrial malignancy—irrespective of endometrial thickness, endometrial morphology, and HRT use. Vascularity index (vascularized area/endometrial area) turned out to be the most useful computer generated power Doppler variable in the multivariate logistic regression model. The 'objective probability' based on endometrial thickness, vascularity index, and HRT use seemed to have a higher capacity than grey scale morphology for detecting small endometrial malignancies (endometrium 5–15 mm). Using the 'objective model', there is a possibility that the probability of endometrial malignancy can be accurately calculated for each individual, even by an inexperienced examiner, by simply finding the most vascularized area of the endometrium and marking the endometrial area. In two studies on women with PMB, the presence of normal or abnormal endometrial blood vessels detected by power Doppler was subjectively evaluated (Amit et al.

2000, Szpurek et al. 2000). Vessels were found in 81%–86% of women with endometrial cancer, but only in 0%–26% of those with normal endometrium (Amit et al. 2000, Szpurek et al. 2000). We detected power Doppler signals in all women with endometrial malignancy and in 83% of those with benign endometrium. The differences in results between the studies are probably to be explained by differences in ultrasound equipment, machine settings, the examiner's experience, and by the lack of standardised criteria for subjective evaluation of endometrial vascularity. To the best of my knowledge, there is no other study in which a researcher has tried to objectively quantify power Doppler signals in the endometrium in order to distinguish benign from malignant endometrium.

However, quantification of power Doppler signals using computer analysis has been used in the diagnosis of cervical carcinoma (Cheng et al. 1999, Wu et al. 2000). Cheng and co-workers (1999), studying women with cervical carcinoma, found that a power Doppler vascularity index (i.e., vascular area divided by tumour area—an index similar to our vascularity index) showed a linear correlation with micro-vessel density and was, to a significant degree, positively correlated with tumour size, depth of stromal invasion, and the presence of lymph node metastases. These results suggest that tumour vascularity, as assessed by power Doppler ultrasound, may be useful in the diagnosis and characterisation of malignancy. It would be worthwhile to further develop the method of using objective quantification of power Doppler signals to correctly diagnose endometrial malignancy. Particularly attractive would be to use the software of the ultrasound system for on-line analysis of power Doppler signals and on-line risk calculation of endometrial malignancy.

Conclusion: Individual risk estimation of endometrial malignancy using a computer-

generated model based on endometrial thickness, vascularity index measured by power Doppler, and HRT use, resulted in better discrimination of benign and malignant endometrium than subjective evaluation of endometrial morphology, — particularly in women with endometrium 5–15 mm.

Until recently, endometrial thickness has been the best method of estimating the risk of endometrial malignancy. Based on the studies in this thesis and the findings of other studies, there is reason to believe that a more individualised and accurate risk estimation can now be made. The model for risk estimation of endometrial malignancy that was constructed in Study V, now needs to be validated. However, new results indicate that there may be other individual factors, aside from HRT use, that may be useful in risk estimation. By combining sonographic research with research from other fields, the risk estimation of endometrial malignancy in women with PMB can, in all probability, be further improved. At the present time, the clinical utility of existing risk estimation models remains uncertain, although they show promise. Until such risk estimation models can be subject to rigorous testing, it remains the case that a conclusive diagnosis can only be made from a histological specimen.

CONCLUSIONS

- If women with PMB and endometrium < 5 mm are to be managed expectantly by ultrasound follow-up, endometrial sampling should be performed in instances where the endometrium grows to ≥ 5 mm, and probably also in case of re-bleeding.
- Endorette[7] and D&C have similar diagnostic properties in women with PMB and endometrium < 7 mm, whereas D&C is superior to Endorette[7] in women with endometrium ≥ 7 mm.
- In women with PMB and endometrium ≥ 5 mm, D&C is an unreliable diagnostic method in the event the patient has focal lesions in the uterine cavity. Operative hysteroscopy is, therefore, a better diagnostic alternative in these women.
- Hydrosonography is equally as good as hysteroscopy in detecting focal lesions in the uterine cavities of women with PMB. However, neither hysteroscopy nor hydrosonography can reliably discriminate between benign and malignant lesions. Distension difficulties at hydrosonography should raise a suspicion of malignancy.
- Power Doppler ultrasound can contribute to a correct diagnosis of endometrial malignancy, especially if the endometrium measures 5–15 mm.
- Intra- and inter-observer reproducibility of endometrial thickness measurements in post-menopausal women are clinically acceptable, and allow reliable discrimination between women with endometrium < 5 mm and ≥ 5 mm.

FUTURE RESEARCH GOALS

- To obtain more evidence on how women with PMB and thin endometrium should be managed.
- To determine if simple sampling devices like Pipelle® or Endorette® are as good as D&C in diagnosing endometrial pathology in women without focal lesions, irrespective of endometrial thickness.
- To determine if the vessel pattern in the endometrium at power Doppler ultrasound examination can be used in the differention of benign and malignant endometrial lesions.
- To prospectively cross-validate the multivariate logistic regression models used to calculate the risk of malignancy
- To make an on-line risk estimation of endometrial cancer among women with PMB (www.riskpreg.com).
- To elucidate the role of genetic factors in the development of endometrial abnormalities.
- To determine the usefulness of 3D ultrasound in the diagnosis of endometrial abnormalities.

CLINICAL GUIDELINES

Selecting biopsy method vs. refraining from sampling

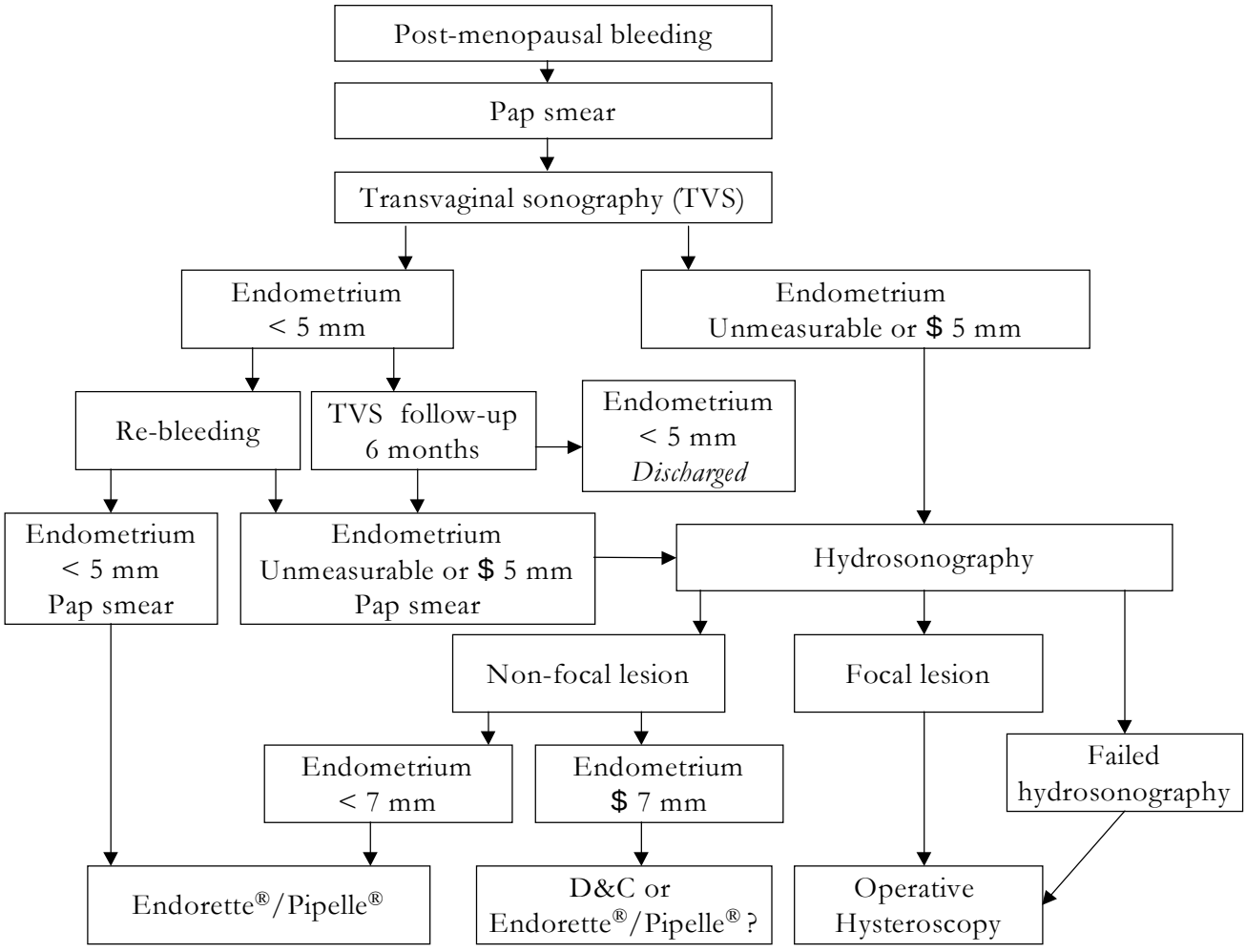


Figure 16.

Risk estimation of endometrial malignancy

Factors associated with increased risk of endometrial cancer	
Sonographic variables	*Other variables*
Endometrial thickness ≥ 5 mm	Woman not using HRT
Irregular endometrial border, inhomogeneous endometrial texture	High body mass index
	Upper body fat distribution
Distension difficulties at hydrosonography	Diabetes mellitus
High vascularity index, i.e., vascularized area/endometrial area, at power Doppler examination	Genetic factors

Figure 17.

SWEDISH SUMMARY
POPULÄRVETENSKAPLIG SVENSK SAMMANFATTNING

Ultraljudets roll vid utredning av postmenopausalblödning

Målsättning

Att ta reda på hur ultraljud bäst används vid utredningen postmenopausalblödning[1] för att individualisera och optimera diagnostiken och behandlingen. Värdet av gråskaleultraljud med eller utan koksaltsinfusion (hydrosonografi)[2] och av "Power Doppler"-ultraljud[3] undersöktes med avsikt att ta reda på om ultraljudsfynden kan användas för 1/ att välja den mest tillförlitliga metoden att ta prov från livmoderslemhinnan, och 2/ att skatta risken för livmodercancer.

Bakgrund

Här presenteras den kunskap som fanns 1995 när avhandlingsarbetet inleddes. Den vanligaste anledningen till att kvinnor efter menopaus söker gynekolog är olaga underlivs blödning. En sådan blödning bör alltid utredas eftersom den kan

1 Postmenopausalblödning är en onormal blödning som inträffat mer än ett år efter det att mensen definitivt upphört.

2 Hydrosonografi innebär att koksalt sprutas in i livmodern via en tunn plastkateter samtidigt som vaginal ultraljudsundersökning utförs. Förändringar i livmoderslemhinnan framträder på detta sätt tydligare. Hydrosonografi tar cirka 5 minuter och kräver inte bedövning.

3 Power Doppler är en ultraljudsteknik som utvecklats de senaste 10 åren. Den avspeglar blodgenomströmningen och kärlrikedomen i ett organ. Blodkärlen framträder i färg.

vara ett tecken på livmodercancer.

Det har visat sig att risken för livmodercancer är relaterad till livmoderslemhinnans tjocklek. Vid vaginal ultraljudsundersökning kan slemhinnan mätas mycket exakt. När slemhinnan är tunn, d.v.s. vid en tjocklek under 5 mm, är risken för livmodercancer mycket låg. Det har därför föreslagits att provtagning från slemhinnan kanske inte är nödvändig, men konsekvenserna av att avstå har inte undersökts. Vi vet därför inte hur vanlig ny blödning eller slemhinnetillväxt är vid postmenopausalblödning med tunn slemhinnan, eller om dessa komplikationer ökar risken för cancer.

När slemhinnan är 5 mm eller mer ökar risken för cancer kraftigt, därför är det nödvändigt av att ta ett prov. Skrapning har under många år varit den gängse metoden för att ta prov från slemhinnan. Det senaste 20 åren har det blivit populärt att använda enkla provtagningsinstrument, t.ex. Endorette®, som ej kräver sövning. Men det finns enstaka studier som visat att såväl skrapning och enkla provtagningsmetoder kan missa polypösa förändringar. Polypösa förändringar kan utgöras av bl.a. muskelknutor, polyper eller cancer. Hur ofta polypösa förändringar missas hos kvinnor med blödning efter menopaus är inte känt. Vi vet heller inte om slemhinnans tjocklek och utseende vid ultraljudsundersökning kan hjälpa oss att välja den mest tillförlitliga provtagningsmetoden.

Hydrosonografi och hysteroskopi[4] kan användas för att ta reda på om det finns polypösa förändringar i livmodern. Men tillförlitligheten hos hydrosonografi att hitta dessa förändringar är inte dokumenterad, dessutom finns det inga studier som

4 Vid hysteroskopi tittar man in i livmodern med en liten kikare. Förändringar i slemhinnan ses direkt och det är möjligt att ta riktade prov under ögats kontroll. Hysteroskopi utförs i narkos eller lokalbedövning.

undersökt om hydrosonografi kan skilja godartade polyper från livmodercancer.

En säkrare uppskattning av risken för livmodercancer, än den som fås genom att mäta slemhinnans tjocklek, skulle kunna hjälpa oss att ytterligare skräddarsy utredningen och behandlingen. Det finns flera tänkbara sätt att öka träffsäkerheten i cancerdiagnostiken med hjälp av ultraljud. Vid gråskaleultraljud kan vissa tecken ge misstanke om cancer, även om tillförlitligheten inte har säkerställts. Dessutom har ”Power Doppler”-ultraljud visat sig ha en mycket god förmåga att hitta små slingriga blodkärl, vilket gör metoden potentiellt lämplig för att hitta kärlnybildningar typiska för cancer. Men det kliniska värdet av ”Power Doppler” i diagnostiken av livmodercancer har inte utforskats.

Livmoderslemhinnans tjocklek har en central betydelse vid handläggandet av postmenopausalblödning. Därför är det viktigt att värdera pålitligheten hos ultraljudsmätningar av slemhinnan. Men detta är inte ordentligt undersökt.

Patienter

Avhandlingen bygger på sex studier omfattande post-menopausala kvinnor *med* blödning (Studie I-VI) eller *utan* blödning (Studie VI). Alla ultraljudsundersökningarna har utförts på Kvinnokliniken vid Universitetssjukhuset MAS i Malmö, av Dr. E.Epstein eller Dr. L.Valentin, under tiden 1995–2001.

Patienter/frivilliga

	Antal kvinnor	Medelålder
Studie I		
Ultraljudsgrupp	48	62
Skrapgrupp	49	65
Studie II	133	65
Studie III och IV	105	66
Studie V	83	66
Studie VI	53	68

Delarbete I-VI; mål, resultat och konklusioner

I. Hur skall kvinnor med tunn slemhinna handläggas? Vad blir konsekvenserna av att avstå från skrapning?

I det första arbetet lottades kvinnor med postmenopausalblödning och slemhinna under 5 mm till antingen ultraljudsuppföljning eller skrapning i narkos. Ny blödning och slemhinnetillväxt var nästan lika vanligt oavsett om skrapning utförts eller ej. Onormal slemhinna förekom endast hos kvinnor där slemhinnan vuxit till 5 mm eller mer.

Slutsats: Om man väljer att följa kvinnor med tunn slemhinna med ultraljudskontroller, så bör provtagning utföras om slemhinnan växer till en tjocklek på 5 mm eller mer.

II. Är Endorette® lika pålitligt som skrapning i narkos? Hur upplever kvinnor Endorette®-provtagning?

I det andra arbetet jämfördes skrapning i narkos med Endorette®, som är ett enkelt provtagningsinstrument för öppenvårdsbruk. Kvinnorna uppgav den smärta de

upplevt vid Endorette®-provtagning, samtidigt som läkaren gjorde en uppskattning av kvinnans smärta. Cirka hälften av kvinnorna upplevde måttlig eller stark smärta vid provtagning. Läkaren underskattade emellertid kvinnans smärta i 2/3 av fallen. Endorette® och skrapning hade samma diagnostiska värde hos kvinnor vars slemhinna var under 7 mm. Skrapning var däremot överlägset Endorette® hos kvinnor med slemhinna på 7 mm eller mer.
Slutsats: Endorette® och skrapning är lika tillförlitliga vid en slemhinna på mindre än 7 mm, medan skrapning är att föredra vid tjockare slemhinna. Kvinnans smärta vid Endorette®-provtagning bör vägas mot risker vid narkos.

III. Hur bra är skrapning på att diagnostisera eller avlägsna polypösa förändringar?
I denna studie undersöktes förekomsten av polypösa förändringar, vid en slemhinna på 5 mm eller mer, samt förmågan hos skapning att diagnostisera och avlägsna dessa förändringar. Åttio procent av kvinnorna hade polypösa förändringar i livmodern, vilket är mer än man tidigare trott. Dessa förändringar utgjordes av bl.a. 50% godartade polyper och 25% cancer. Skapning missade drygt hälften av polyperna och var tionde cancer, vilket är anmärkningsvärt. Korrekt diagnos erhölls genom hysteroskopi med riktad provtagning.
Slutsats: Vid förekomst av polypösa förändringar är skrapning en opålitlig provtagningsmetod. Om det finns polypösa förändringar i livmodern är hysteroskopi med riktad provtagning att föredra.

IV. Kan hydrosonografi hjälpa oss att hitta polypösa förändringar? Går det att skilja på godartade förändringar och cancer med hjälp av hydrosonografi?
I det fjärde arbetet undersökte vi förmågan hos hydrosonografi att hitta polypösa förändringar samt förmågan hos hydrosonografi att skilja godartade förändringar från cancer. Överensstämmelsen mellan hydrosonografi och hysteroskopi var

nästan perfekt (96%) när det gällde att hitta polypösa förändringar. Men hydrosonografi kunde ej tillförlitligt avgöra om en polypös förändring var cancer. Däremot innebar en oförmåga att fylla livmodern med vätska vid hydrosonografi en kraftig indikation på cancer (7 gånger ökad risk).

Slutsats: Hydrosonografi kan med fördel användas för att diagnostisera polypösa förändringar. Alla polypösa förändringar bör betraktas som potentiellt elakartade — och skall således avlägsnas helt. Oförmåga att fylla livmodern med vätska vid hydrosonografi bör betraktas som ett nytt kriterium vid diagnostik av livmodercancer.

V. Kan "Power Doppler" ultraljud hjälpa oss att bedöma risken för livmodercancer?

I den femte studien undersökte vi om "Power Doppler"-ultraljud av kunde bidra till att bedöma risken för cancer. Cancerrisken hos varje kvinna beräknades med matematiska modeller som baserades på individuella faktorer, samt fynden vid gråskaleultraljud och vid "Power Doppler". Vi fann att kärlrikedomen i slemhinnan, mätt med "Power Doppler", hade betydelse för cancerrisken — ju större del av slemhinnan som var kärlförsedd desto större risk för cancer. "Power Doppler" visade sig ha en högre förmåga än gråskaleultraljud att hitta tidig cancer. Hormonanvändning var den enda individuella faktorn som hade betydelse för cancerrisken. Hormonanvändning (gulekroppshormon + östrogen, i kombination) minskade risken för cancer.

Slutsats: För första gången är det visat att "Power Doppler" kan bidra till en säkrare och bättre diagnostik av livmodercancer. Speciellt lovande tycks metoden vara då det gäller att hitta tidig cancer.

VI. Kan vi lita på mätningar av slemhinnetjockleken?

I denna studie undersöktes tillförlitligheten vid slemhinnetjockleks mätningar med

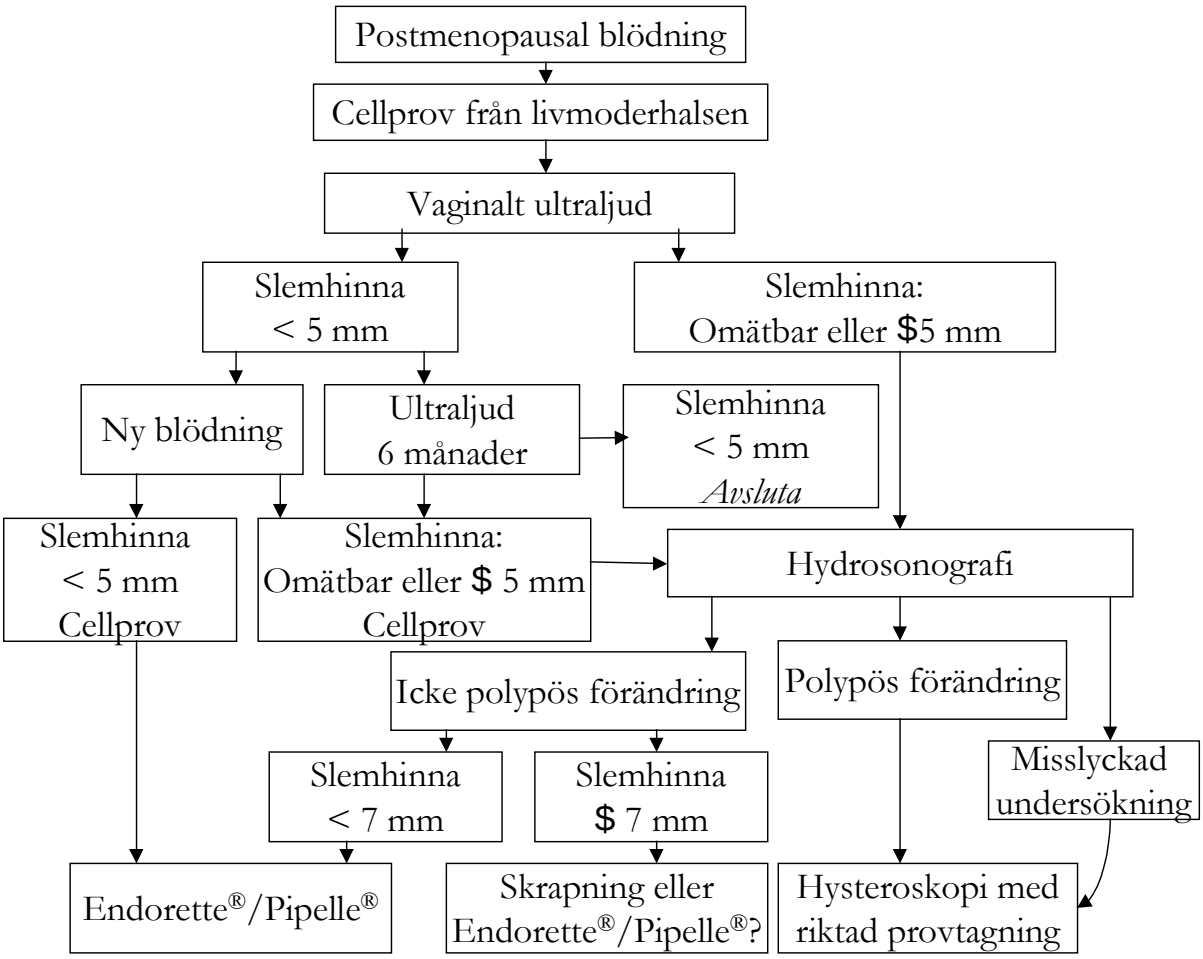
vaginalt ultraljud. Båda underökarna kunde tillfredsställande upprepa sina mätningar oavsett slemhinnans tjocklek. Dessutom var överensstämmelsen mellan de båda undersökarnas mätresultat utmärkt. *Slutsats:* Mätningar av slemhinnetjockleken med vaginalt ultraljud är kliniskt tillförlitliga.

Klinisk betydelse av avhandlingen

Denna avhandlig tar ett samlat grepp på handläggandet av blödning efter menopaus, där ultraljud visat sig ha en central roll. Med hjälp av resultaten från våra studier har de flesta viktiga frågeställningar kunnat besvaras och kliniska riktlinjer utformas (se nedan). Efter handledd träning kan dessa riktlinjer användas av alla gynekologer. Kvinnor med blödning efter menopaus kan därmed erbjudas en individuellt anpassad utredning och behandling. Onödig provtagning kan undvikas, samtidigt som patientsäkerheten ökas genom att valet av provtagningsmetod anpassas till ultraljudsfynden. Genom att välja den mest lämpliga metoden kan såväl läkare och patient känna tillit till utredningen, eftersom risken för att feldiagnoser minimeras. Fram till idag har mätning av slemhinnetjockleken varit den bästa metoden för att bedöma risken för livmodercancer. Genom att skatta cancerrisken kan å ena sidan fall med misstänkt cancer högprioriteras för ett snabbt handläggande, å andra sidan kan ytterligare utredning undvikas hos kvinnor med låg risk för cancer men med hög risk för narkoskomplikationer. Två helt nya sätt att bedöma cancerrisken presenteras i denna avhandling, vilka var och en för sig bidrar till en säkrare bedömning. Vi har bland annat visat att "Power Doppler" har en högre förmåga än gråskaleultraljud att korrekt diagnosticera tidig livmodercancer. Riskbedömningen av livmodercancer kan sannolikt i framtiden ytterligare förbättras, dels genom att vidareutveckla "Power Doppler" och dels genom att kombinera ultraljudsfynden med bedömning av olika individuella faktorer. Hormonanvändning visade sig vara en sådan faktor. Vi fann nämligen att

livmodercancer var tio gånger vanligare hos kvinnor som inte använde hormoner (östrogener+ gulekroppshormon) jämfört med hos dem som gjorde det. Andra tänkbara faktorer som skulle kunna förbättra bedömningen är t.ex. övervikt, sockersjuka och genetiska faktorer. Samarbete mellan olika discipliner kan påskynda en ytterligare förbättrad diagnostik

Riktlinjer — utredning av postmenopausalblödning



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APPENDIX

Study I:

Re-bleeding and endometrial growth in women with post-menopausal bleeding and endometrium < 5 mm managed by dilatation and curettage or ultrasound follow-up. A randomised controlled study.

Study II:

Comparison of Endorette[7] and dilatation and curettage for sampling of the endometrium in women with post-menopausal bleeding.

Study III:

Dilatation and curettage fails to detect most focal lesions in the uterine cavity in women with post-menopausal bleeding.

Study IV:

Transvaginal sonography, saline contrast sonohysterography and hysteroscopy for the investigation of women with post-menopausal bleeding and endometrium ≥ 5 mm.

Study V:

An algorithm including results of grey scale and power Doppler ultrasoundexamination to predict endometrial malignancy in women with post-menopausal bleeding.

Study VI:

Reproducibility of endometrial measurements in post-menopausal women.