Ultrasound and Menstrual History in Predicting Endometrial Hyperplasia in Polycystic Ovary Syndrome

Anthony P. Cheung, MBBS, MPH

OBJECTIVE: **To assess the role of endometrial thickness on vaginal ultrasound assessment and menstrual history in predicting endometrial hyperplasia in women with polycystic ovary syndrome (PCOS) who presented with infertility due to anovulation.**

METHODS: **This was a prospective study in a university referral-based fertility and endocrine clinic. Fifty-six women with PCOS presenting with infertility due to anovulation underwent both vaginal ultrasound assessments and endometrial biopsies. The main outcome measures were the predictive value of sonographic endometrial thickness (primary objective) and the menstrual history with other clinical characteristics (secondary objective) for proliferative endometrium and endometrial hyperplasia in logistic regression analysis. Their predictive value was further examined by receiver operating characteristic curve analysis.**

RESULTS: **Thirty-six PCOS patients (64.3%) had proliferative endometrium and 20 (35.7%) had endometrial hyperplasia. Five of the latter (25%) had cytologic atypia. Endometrial thickness less than 7 mm or intermenstrual interval less than 3 months (corresponding to more than four menstrual periods yearly) was associated with proliferative endometrium only. The endometrial thickness correlated positively with endometrial hyperplasia ($P = .018$) and, together with the average intermenstrual interval, were significant predictors of endometrial hyperplasia ($P < .001$).**

CONCLUSION: **These findings point to the usefulness of obtaining a detailed menstrual history in women with PCOS by identifying those at increased risk of endometrial hyperplasia and who require an endometrial biopsy. The endometrial thickness corroborates this clinical impression and is particularly useful when the menstrual history is uncertain. Endometrial hyperplasia in this population is effectively excluded when the endometrial thickness is less than 7 mm. (Obstet Gynecol 2001;98:325–31. © 2001 by the American College of Obstetricians and Gynecologists.)**

From the Department of Obstetrics and Gynaecology, University of Alberta, Edmonton and University of British Columbia, Vancouver, British Columbia, Canada.

Chronic anovulation and hyperandrogenism are clinical hallmarks of women with polycystic ovary syndrome (PCOS). Owing to anovulation, the endometrium in PCOS is exposed to the prolonged mitogenic effects of estrogen, unopposed by the inhibitory effects of progesterone present in the luteal phases of normal menstrual cycles. It is therefore not surprising that anovulation and PCOS are recognized risk factors for endometrial hyperplasia, with or without cytologic atypia.[1,2] Whether anovulation and PCOS translate into risk factors for endometrial adenocarcinoma as well remains an open question, in part because of the rare occurrence of the latter in young women.[2–6] In 1970, Chamlian and Taylor[1] found that 25% of the 97 cases of endometrial hyperplasia in women younger than 35 years presenting with irregular uterine bleeding had sclerocystic ovaries (the criterion used to support the diagnosis of PCOS at that time). Although this case series retrospectively identified an increased prevalence of PCOS in women found to have a histologic diagnosis of endometrial hyperplasia, the converse (ie, the frequency of endometrial hyperplasia in women with PCOS presenting with infertility due to anovulation) is unknown. Specifically, the relevant clinical question is whether all PCOS women require an endometrial biopsy to exclude endometrial disease before ovulation-induction therapy is initiated. A corollary question is: Are there clinical predictors that can identify those more likely to have endometrial hyperplasia? Currently, no clear clinical guidelines are available to determine when a detailed evaluation of the endometrium is indicated in this population.

Pelvic ultrasound assessment has been widely used to screen for the presence of polycystic ovaries as part of the diagnostic criteria for PCOS in European centers, particularly in the United Kingdom.[7] In addition, a baseline pelvic ultrasound assessment is invaluable in ruling out any pre-existing ovarian cysts before ovulation-induction therapy, especially if obesity (a common feature of PCOS) compromises the usefulness of a routine pelvic examination. In postmenopausal women with uterine

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bleeding, the endometrial thickness on vaginal ultrasound assessment has been positively correlated with the presence of endometrial abnormalities, and curettage can be avoided if the endometrial thickness is no more than 4 mm.[8] The primary objective of the current study was to determine whether the endometrial thickness could similarly predict endometrial abnormalities in women with PCOS whose primary presentation was infertility due to anovulation. Accordingly, before ovulation-induction therapy, the endometrial thickness was measured during the baseline vaginal ultrasound assessment of the ovaries and the pelvis and was immediately followed by an endometrial biopsy. In addition, predictive values for other clinical characteristics, particularly the menstrual history, were assessed.

MATERIALS AND METHODS

This was a prospective study in a university referral-based fertility and endocrine clinic. Because no clear clinical guidelines are available to suggest when an endometrial biopsy should be done, 56 consecutive women with PCOS who presented with infertility due to anovulation underwent vaginal ultrasound assessments and endometrial biopsies as part of their clinical work-up. The sensitivity and specificity of the endometrial biopsy using the Pipelle (Unimar, Wilton, CT) device (relative to D&C or hysterectomy) have been reported to be at least 0.95.[9–11] Hence, relative to the "reference" test (endometrial biopsy), 14 women with endometrial abnormalities and 27 with normal endometrial histologic findings were required for the "new" test (endometrial thickness) to detect a difference of no less than 0.20 for sensitivity and no less than 0.10 for specificity ($\alpha_1 = 0.05$ and power of 90% for paired observations)[12] (Fried RE, Appel LJ. How many patients are necessary to assess test performance? [letter; comment]. JAMA 1990;264:2074–5). These patients all had oligoamenorrhea and clinical and/or biochemical evidence of hyperandrogenism. Because infertility was the primary problem, all had not practiced contraception for more than 1 year. In the investigator's clinical practice, a blood test for progesterone, as well as TSH and prolactin, was routinely collected at the time of the first consultation. For those who reported recent menstrual bleeding, the blood tests were delayed until 22 days from the onset of menstruation. If the serum progesterone level was no more than 3 nmol/L (up to 1 ng/mL), the laboratory staff were instructed to measure the testosterone, androstenedione, dehydroepiandrosterone sulfate levels, as well as LH, FSH, and estradiol, on the same serum sample to complete the laboratory work-up. Androstenedione and dehydroepiandrosterone sulfate were measured using radioimmunoassay kits from Diagnostic Systems Laboratories Inc. (Webster, TX) and Diagnostic Products Corp. (Los Angeles, CA), respectively; the remaining hormones were measured using immunometric techniques (Ciba Corning Diagnostics, Essex, United Kingdom).

The progesterone results were routinely available within 1 working day. All subjects had progesterone levels in the anovulatory range of up to 3 nmol/L within 3 days before the vaginal ultrasound examination and the endometrial biopsy, which were done as office procedures. The endometrial thickness was taken as the widest distance from the reflective interface between the endometrium and myometrium of one side to the opposing side on a sagittal view of the uterus[13,14] using a 5-MHz linear-array vaginal transducer (UltraMark 4 Plus, ATL, Bothell, WA). The endometrial biopsy was performed with the Pipelle device (Unimar) immediately after sonographic examination. All vaginal ultrasound assessments and endometrial biopsies were performed by the investigator. The endometrial specimens were sent to the Department of Pathology at the University of Alberta Hospital for histologic evaluation. Two main histologic groups were identified: "proliferative endometrium" and "endometrial hyperplasia." Simple or complex hyperplasias with or without cytologic atypia were combined within the "endometrial hyperplasia" group because of the relatively small number in each of the hyperplastic subcategories.

After the procedures, the subjects were prescribed oral medroxyprogesterone acetate 10 mg daily for an average of 10 days. Ovulation-induction therapy was started on day 3 of bleeding induced by medroxyprogesterone acetate unless endometrial hyperplasia with cytologic atypia was diagnosed. Those with cytologic atypia were treated with medroxyprogesterone acetate 10 mg daily for 14 days of each month for 3 months, after which an endometrial biopsy was repeated. One case of persistent atypia was managed by additional medroxyprogesterone acetate treatment and a detailed hysterocopic examination and biopsy-excision under direct visualization followed by curettage. Proliferative endometrium was identified in all subsequent follow-up assessments.

The clinical and hormonal characteristics of the two histologic groups were reported as the mean ± standard error of the mean. Continuous variables were assessed by the Mann-Whitney *U* test, since the normality of the distribution was not assumed, and categorical variables by the χ^2 test. An identical pattern of significant results was obtained when the continuous variables were reanalyzed using the unpaired *t* test. Simple logistic regression analysis was first used to test the a priori hypothesis that the endometrial thickness correlated positively with the finding of endometrial hyperplasia on the endometrial biopsy. Stepwise logis-

Table 1. Clinical and Hormonal Characteristics

Characteristic	Proliferative endometrium (n = 36) Mean	SEM	Hyperplasia (n = 20) Mean	SEM	P
Age (y)	29.50	0.67	32.15	1.04	.042
Menarche (y)	12.76	0.30	13.30	0.43	.424
Onset at menarche* (%)	58.33		80.00		.143
Previous OC use* (%)	75.00		70.00		.758
Years of OC use†	2.80	0.57	2.99	3.17	.802
Years of OC use‡	3.74	0.67	4.00	0.85	.761
Years since last OC†	6.09	0.88	9.30	1.56	.072
Years since last OC‡	3.89	0.41	6.07	1.06	.066
Smoking* (%)	19.44		20.00		.999
Cigarettes per wk	3.11	1.14	2.05	1.15	.549
Body mass index	32.51	1.35	33.19	1.79	.905
Ferriman-Gallwey score	8.94	0.93	7.25	0.94	.411
Systolic BP (mmHg)	126	3	120	4	.256
Diastolic BP (mmHg)	80	2	79	3	.897
PCOs on VUS* (%)	94.44		90.00		.288
LH (IU/L)	15.15	1.19	12.60	1.27	.186
FSH (IU/L)	5.77	0.44	5.92	0.40	.502
LH FSH ratio	2.73	0.20	2.21	0.21	.145
Progesterone (nmol/L)	1.56	0.13	1.31	0.06	.053
Estradiol (pmol/L)	240	24	228	29	.809
Testosterone (nmol/L)	2.41	0.15	2.20	0.22	.281
Androstenedione (nmol/L)	8.91	0.83	8.64	0.99	.914
DHEAS (μmol/L)	6.19	0.53	5.37	0.67	.263
TSH (mU/L)	2.47	0.40	1.87	0.20	.959
Prolactin (μg/L)	8.96	0.80	6.90	0.60	.117

SEM = standard error of the mean; OC = oral contraceptive; BP = blood pressure; PCOs = polycystic ovaries; VUS = vaginal ultrasonography; DHEAS = dehydroepiandrosterone sulfate.

To convert the hormone levels to conventional units, divide the appropriate values from Table 1 by the following factors: LH and FSH (mIU/mL), 1; progesterone (ng/mL), 3.18; estradiol (pg/mL), 3.671; testosterone (ng/mL), 3.467; androstenedione (ng/mL), 3.492; DHEAS (μg/mL), 0.02714; TSH (μU/ml), 1; and, prolactin (ng/mL), 1.

* Percentage of women who had onset of irregular menses from menarche, who previously used OCs, who smoked or who had features of PCOs in at least one ovary on VUS.

† Included all patients; adjusted for 15 patients who had never used OCs.

‡ Included only patients who had a history of OC use (n = 41).

tic regression analysis was then used to test the following factors as potential predictors of endometrial hyperplasia: age, body mass index, endometrial thickness, average intermenstrual interval in months (the inverse of menstrual frequency, defined as the average number of menses per year), menses–biopsy interval in weeks (the interval from the onset of the last menses to vaginal ultrasound assessment and endometrial biopsy) and last oral contraceptive (OC) use (the number of years since the last use of OC). For those who had never used OCs, the duration of probable unopposed estrogen exposure due to anovulation was calculated by subtracting from the current age, the age at menarche, and 1.5 years for each prior childbirth. Fifteen women had never taken OCs and only four of these required adjustment for prior childbirths. In logistic regression analysis, the McFadden's Rho-square reported is a transformation of the likelihood ratio statistic intended to mimic an R-square in linear regression. It is always between 0 and 1, and a higher Rho-square corresponds to more significant results. The Rho-square tends to be much lower than R-square, however, and values between 0.20 and 0.40 are considered very satisfactory.[15] The test performance of endometrial thickness and its comparison with the menstrual pattern were also evaluated by receiver operating characteristic (ROC) curve analysis.[16,17] Statistical and ROC curve analysis was performed using Systat 8.0 (Scientific Package for Social Sciences Inc., 1998, Chicago, IL) and MedCalc 6.0 (MedCal Software, 2000, Mariakerke, Belgium), respectively. The level of significance was defined at a P value of less than .05.

RESULTS

The clinical and hormonal data are summarized in Table 1. Thirty-six endometrial biopsies (64.3%) showed proliferative endometrium only and 20 (35.7%) showed endometrial hyperplasia. Of the 20 cases of endometrial hyperplasia, 12, three, and five cases were classified as

Table 2. Sonographic Findings and Menstrual Pattern

	Proliferative endometrium (n = 36)			Endometrial hyperplasia (n = 20)			
	Median	Mean	SEM	Median	Mean	SEM	P*
Endometrial thickness (mm)	7.00	7.70	0.40	9.00	9.50	0.60	.017
Menstrual frequency per year	4.00	3.65	0.23	1.75	1.68	0.29	<.001
Intermenstrual interval (mo)	3.00	3.92	0.39	7.5	10.45	2.23	<.001
Menstrual-biopsy interval (wk)	9.00	12.28	2.82	24.00	35.90	10.30	<.001

SEM = standard error of the mean.

* Mann-Whitney U test. No endometrial hyperplasia was observed if the endometrial thickness was less than 7 mm or the intermenstrual interval was less than 3 months. For women with more complex menstrual histories, see text.

simple hyperplasia, complex hyperplasia, and hyperplasia with cytologic atypia, respectively. No cases of endometrial adenocarcinoma were identified in this patient population. There were no differences in the age of onset at menarche (range 9.5–18 and 11–18 years for proliferative endometrium and hyperplasia, respectively). The mean age of the women with endometrial hyperplasia was older than that of women with proliferative endometrium (Table 1), with a range of 23–41 years and 21–39 years, respectively. The five women who had endometrial hyperplasia with cytologic atypia (reported as focal in nature) included the three oldest in the study: two were 30 years, two were 39 years, and one was 40 years of age. Four of these five women had reported amenorrhea for 1–4 years; three had never used OCs; the remaining two had not used OCs for more than 10 years. Women with endometrial hyperplasia had longer intervals since the last OC use than those with proliferative endometrium but differences were only of marginal statistical significance (Table 1). Among the OC users, the range for the years since last OC use was 2–8 years and 2–13 years for those with proliferative endometrium and hyperplasia, respectively. There were no other significant differences in the characteristics listed in Table 1.

On vaginal ultrasound assessment, the endometrium associated with chronic anovulation in women with PCOS lacked the typical "triple-line" appearance seen in the follicular phase of a normal menstrual cycle.[13,14] Instead, a homogenous hyperechoic pattern was invariably observed. The results comparing the two main histopathologic findings according to the endometrial thickness, menstrual frequency, intermenstrual interval, and menses-biopsy interval are summarized in Table 2. Women with hyperplasia had a significantly thicker endometrium, fewer menstrual periods per year, longer intermenstrual intervals, and longer menses-biopsy intervals preceding the endometrial biopsy. Fourteen subjects had more complex menstrual histories, reporting intermenstrual intervals of 2–3 months, as well as irregular, prolonged bleeding episodes of 2–8 weeks. Of these, two women with intermenstrual intervals of 3 months had endometrial hyperplasia. Most of the endometrial hyperplasia occurred in women with fewer than three episodes of menstrual flow per year (a corresponding interval between menses of 4 months or longer) on average.

In simple logistic regression analysis, the endometrial thickness was positively correlated with endometrial hyperplasia (P = .018). Using stepwise logistic regression analysis, only the endometrial thickness and intermenstrual interval were found to be significant predictors of endometrial hyperplasia (P < .001; McFadden's Rho-square = .358). The odds ratio (OR) and 95% confidence interval (CI) of the relevant variables are detailed in Table 3. Last OC use was positively correlated with hyperplasia only when the 41 patients who had a prior history of OC use were analyzed separately (P = .038, OR 1.279, 95% CI 1.013, 1.615).

The endometrial thickness and intermenstrual interval (the two significant variables in the stepwise regression analysis) were further evaluated in the ROC curve analysis. In parallel to the findings from the logistic

Table 3. Predictors of Endometrial Hyperplasia

Independent variables	Odds ratio	95% Confidence interval	P
Age	1.061	1.273, 0.885	.520
Body mass index	0.983	1.082, 0.893	.723
Endometrial thickness	1.346	1.785, 1.015	.038*
Intermenstrual interval	1.432	1.782, 1.151	.001*
Menses-biopsy interval	0.981	1.033, 0.932	.463
Last oral contraceptive use	1.011	1.143, 0.894	.865

* Significant results from stepwise logistic regression.

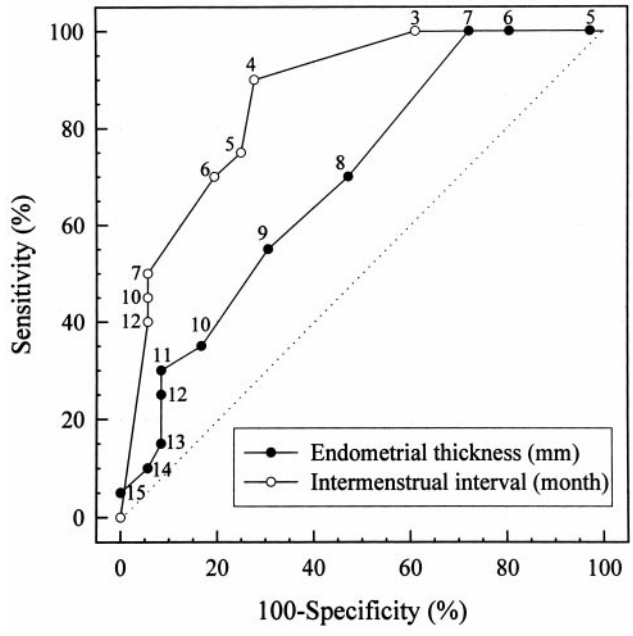

Figure 1. Receiver operating characteristic curves for endometrial thickness and intermenstrual interval. The closer the ROC plot is to the upper left corner, the higher the overall accuracy of the test. When the variable under study cannot distinguish between the two groups, the area under the ROC curve is equal to 0.5 (*diagonal straight line*). For details, see text.

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regression analysis, the areas under the ROC curves for endometrial thickness and intermenstrual interval were both greater than 0.5 (Figure 1). The areas under the ROC curves for the intermenstrual interval and endometrial thickness were, respectively, 0.86 (95% CI 0.74, 0.94) and 0.69 (95% CI 0.55, 0.81); the difference in area was at the level of statistical significance ($P = .051$). Although this confirmed that these two variables under study could distinguish the two histologic groups, there was obviously a trade-off between sensitivity and specificity according to the cutoff points chosen (Figure 1).

DISCUSSION

This study demonstrated that in anovulatory, infertile women with PCOS, endometrial thickness less than 7 mm or intermenstrual interval less than 3 months (more than four menstrual periods per year) is associated with proliferative endometrium only (Table 2). Hence, when these criteria are present, no endometrial hyperplasia is anticipated. In contrast, the risk of finding endometrial hyperplasia on endometrial biopsy is estimated to rise by 34.6% (OR 1.346) when, for example, the endometrial thickness increases from 8–9 to 9–10 mm (holding cycle length constant). Similarly, the risk of endometrial hyperplasia is predicted to rise by 43.2% (OR 1.432) when the duration of amenorrhea increases from 5 to 6 months if the endometrial thickness is held constant. In this prospective cohort, the prevalence of endometrial hyperplasia was 36% (20 of 56); of these, 25% (five of 20) showed focal cytologic atypia. Hence, the main rationale for endometrial biopsy screening is to exclude the presence of atypia, which carries a high risk of progression to carcinoma. In one retrospective study, 23% (11 of 48) of cases of untreated hyperplasia with atypia progressed to carcinoma but only 2% (two of 122) of the cases of untreated hyperplasia without atypia did so.[18]

Although the mean values for age and the menses-biopsy interval were significantly greater in women with hyperplasia (Tables 1 and 2), the predictive value of either on regression analysis had no clinical impact. The predictive value of age was influenced by a greater number of older women in the hyperplasia group. The menses-biopsy interval was confounded by the occurrence of irregular bleeding independent of the history of oligoamenorrhea. Twelve of the 14 women reporting varying intermenstrual intervals of 2–3 months, but also irregular, prolonged bleeding episodes of 2–8 weeks, had proliferative endometrium only. In contrast, the longer menses-biopsy intervals (1, 1.5, 1.5, and 4 years) in the absence of any dysfunctional uterine bleeding in four of the five subjects with atypia were equivalent to exceedingly long intermenstrual intervals. Hence, all four would have been selected for endometrial biopsy on this basis according to the regression model, regardless of the menses-biopsy interval.

Thus, although the primary objective of this study was to evaluate the usefulness of endometrial thickness on ultrasound scanning, the menstrual pattern proved to be a more useful screening tool than the endometrial thickness, as illustrated by the larger area under the ROC curve (Figure 1). Indeed, using an endometrial thickness of up to 7 mm as the cutoff threshold for endometrial hyperplasia, the sensitivity, specificity, and false-positive and false-negative predictive rate would be 100%, 27.8%, 56.5%, and 0%, respectively; using an average intermenstrual interval of up to 3 months as the cutoff threshold, the corresponding values would be 100%, 38.9%, 52.4%, and 0%. Taken together, this reinforces the importance of obtaining a detailed history of the menstrual pattern in selecting women with PCOS for endometrial biopsy. Endometrial thickness, on the other hand, further supports the clinical impression and is particularly useful when the menstrual history is unclear. Hence, although an average intermenstrual interval of less than 3 months (or more than four menstrual periods per year) is asso-

ciated with finding proliferative endometrium only, a recent onset of more irregular or prolonged bleeding will invalidate this guideline. In this situation, an endometrial biopsy can be avoided if the endometrial thickness is less than 7 mm.

The criteria derived from this study are only applicable so far to women with PCOS who present with anovulatory infertility, who have at least 2 years of irregular, infrequent menstrual periods by history, and who presumably have an increased risk of unopposed estrogen exposure without the benefits of regular exogenous progestin exposure (OC or cyclic progestogen). Although intuitively it seems that an interval between "menses" of less than 3 months ought not to be associated with hyperplasia, it is well recognized that the occurrence of "menses" in women with PCOS does not necessarily indicate a preceding ovulation. Potential limitations in applying menstrual history criteria remain. As mentioned previously, the presence of irregular or prolonged bleeding would confound these general guidelines and, from a clinical perspective, these situations would require individualized assessments. An endometrial thickness greater than 7 mm or intermenstrual interval of more than 3 months can be associated with either a proliferative endometrium or endometrial hyperplasia. An endometrial biopsy would be indicated to establish the diagnosis under these circumstances.

Subtle misclassification of the histopathologic findings might exist since the endometrial biopsy specimens were read by a team of anatomic pathologists in a university department and not necessarily by a gynecologic pathology subspecialist. However, in ambiguous cases, intra- and interdepartmental consultations were clearly recorded in the reports. It can be argued that such problems reflect clinical practice and, therefore, represent the effectiveness in an actual clinical setting rather than the idealized efficacy associated with a research environment. Finally, the number of patients in this study was relatively small. Nevertheless, the findings provide a preliminary framework to begin establishing some clinical guidelines as to when detailed evaluation of the endometrium is indicated in women with PCOS presenting for ovulation-induction therapy and to emphasize the clinical importance of obtaining a detailed gynecologic history and the usefulness of routine measurement of the endometrial thickness as part of the baseline ultrasound assessment.

REFERENCES

1. Chamlian DL, Taylor HB. Endometrial hyperplasia in young women. Obstet Gynecol 1970;36:659–66.
2. Ho SP, Tan KT, Pang MW, Ho TH. Endometrial hyperplasia and the risk of endometrial carcinoma. Singapore Med J 1997;38:11–5.
3. Niwa K, Imai A, Hashimoto M, et al. A case-control study of uterine endometrial cancer of pre- and post-menopausal women. Oncol Rep 2000;7:89–93.
4. Gregorini SD, Lespi PJ, Alvarez GR. Endometrial carcinoma with polycystic ovaries. Report of two cases in women younger than 40 years old. Medicina 1997;57: 209–12.
5. Dahlgren E, Friberg LG, Johansson S, et al. Endometrial carcinoma. Ovarian dysfunction–A risk factor in young women. Eur J Obstet Gynecol Reprod Biol 1991;41: 143–50.
6. Aksel S, Wentz AC, Jones GS. Anovulatory infertility associated with adenocarcinoma and adenomatous hyperplasia of the endometrium. Obstet Gynecol 1974;43: 386–91.
7. Adams J, Polson DW, Franks S. Prevalence of polycystic ovaries in women with anovulation and idiopathic hirsutism. BMJ (Clin Res Ed) 1986;293:355–9.
8. Karlsson B, Granberg S, Wikland M, et al. Transvaginal ultrasonography of the endometrium in women with postmenopausal bleeding–a Nordic multicenter study. Am J Obstet Gynecol 1995;172:1488–94.
9. Droegemueller W. Diagnostic procedures–Imaging, endometrial sampling, endoscopy: Indications, contraindications and complications. In: Mishcll DR, Stenchever SM, Droegemueller W, Herbst AL, eds. Comprehensive gynecology. 3rd ed. St. Louis: Mosby-Year Book, Inc., 1997.
10. Ben-Baruch G, Seidman DS, Schiff E, Moran O, Menczer J. Outpatient endometrial sampling with the Pipelle curette. Gynecol Obstet Invest 1994;37:260–2.
11. Schneider J, Centeno MM, Ausin J. Use of the Cornier pipelle as the only means of presurgical histologic diagnosis in endometrial carcinoma: Agreement between initial and final histology. Eur J Gynaecol Oncol 2000;21:74–5.
12. Arkin CF, Wachtel MS. How many patients are necessary to assess test performance? JAMA 1990;263:275–8.
13. Sakamoto C. Sonographic criteria of phasic changes in human endometrial tissue. Int J Gynaecol Obstet 1985;23: 7–12.
14. Fleischer AC, Kalemeris GC, Entman SS. Sonographic depiction of the endometrium during normal cycles. Ultrasound Med Biol 1986;12:271–7.
15. Hensher D, Johnson LW. Applied discrete choice modelling. London: Croom Helm, 1981.
16. Zweig MH, Campbell G. Receiver-operating characteristic (ROC) plots: A fundamental evaluation tool in clinical medicine [published erratum appears in Clin Chem 1993; 39:1589]. Clin Chem 1993;39:561–77.
17. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology 1983;148:839–43.
18. Kurman R, Kaminski P, Norris H. The behavior of endo-

metrial hyperplasia. A long-term study of "untreated" hyperplasia in 170 patients. Cancer 1985;56:403–12.

Address reprint requests to: Anthony P. Cheung, MBBS, MPH, Department of Obstetrics and Gynaecology, University of British Columbia, Division of Reproductive Endocrinology and Infertility, 2nd Floor Willow Pavilion, Vancouver Hospital and Health Sciences Centre, 855 West 12th Avenue, Vancouver, British Columbia V5Z 1M9, Canada; E-mail: apcheung@interchange.ubc.ca.

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