Accuracy of Hysteroscopy in the Diagnosis of Endometrial Cancer and Hyperplasia

A Systematic Quantitative Review

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Context Hysteroscopy (direct endoscopic visualization of the endometrial cavity) is used extensively in the evaluation of common gynecologic problems, such as menorrhagia and postmenopausal bleeding. However, there is a continuing debate about the value of this technology in the diagnosis of serious endometrial disease.

Objective To determine the accuracy of hysteroscopy in diagnosing endometrial cancer and hyperplasia in women with abnormal uterine bleeding.

Data Sources Relevant articles were identified through searches of the Cochrane Library, MEDLINE, and EMBASE (1984-2001), manual searches of bibliographies of known primary and review articles, and contact with manufacturers.

Study Selection Studies were selected blindly, independently, and in duplicate if accuracy of hysteroscopy was estimated in women with abnormal uterine bleeding, using histopathologic findings as a reference standard. Our search identified 3486 articles; 208 of these were deemed to be potentially eligible and were retrieved for detailed data extraction. Sixty-five primary studies were analyzed, including 26346 women.

Data Extraction Data were abstracted on characteristics and quality from each study. Results for diagnostic accuracy were extracted to form 2×2 contingency tables separately for endometrial cancer and endometrial disease (cancer, hyperplasia, or both). Pooled likelihood ratios (LRs) were used as summary accuracy measures.

Data Synthesis The pretest probability of endometrial cancer was 3.9% (95% confidence interval [CI], 3.7%-4.2%). A positive hysteroscopy result (pooled LR, 60.9; 95% CI, 51.2-72.5) increased the probability of cancer to 71.8% (95% CI, 67.0%-76.6%), whereas a negative hysteroscopy result (pooled LR, 0.15; 95% CI, 0.13-0.18) reduced the probability of cancer to 0.6% (95% CI, 0.5%-0.8%). There was statistical heterogeneity in pooling of LRs, but an explanation for this could not be found in spectrum composition and study quality. The overall accuracy for the diagnosis of endometrial disease was modest compared with that of cancer, and the results were heterogeneous. The accuracy tended to be higher among postmenopausal women and in the outpatient setting.

Conclusion The diagnostic accuracy of hysteroscopy is high for endometrial cancer, but only moderate for endometrial disease (cancer or hyperplasia).

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MENORRHAGIA, UNSCHEDULED bleeding while undergoing hormone replacement therapy, and postmenopausal bleeding are common gynecologic problems.[1,2] The main aim of investigations for abnormal uterine bleeding is to exclude serious pathological intrauterine conditions, such as endometrial cancer and hyperplasia.[3] Traditionally, abnormal uterine bleeding has been investigated with dilation and curettage, but now there is a trend toward minimally invasive investigations using outpatient endometrial biopsy, ultrasound scan, and hysteroscopy.[2,4]

Hysteroscopy (direct endoscopic visualization of the endometrial cavity) is considered a safe and acceptable procedure and is used extensively in Europe and North America for the evaluation of uterine bleeding disorders.[5-10] Recent advances in instrumentation have allowed hysteroscopy to be performed in an ambulatory setting, further increasing its use in gynecologic practice.[11] However, there is a continuing debate about the value of hysteroscopy in diagnosis of serious endometrial diseases, such as cancer, hyperplasia, or both. This is because individual studies on histopathologic validation of endoscopic visual interpretation are small, leading to imprecise and heterogeneous estimates of accuracy.[12] Furthermore, the accuracy of hysteroscopic diagnosis may vary according to menopausal status and clinical setting (eg, in-

See also Patient Page.

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patient or outpatient). Therefore, we undertook a quantitative systematic review to obtain more precise accuracy estimates[13] and to explore reasons for heterogeneity.

METHODS

Identification of Studies

General bibliographic databases (MEDLINE and EMBASE) were searched from January 1984 to December 2001. The medical subject heading (MeSH) and text words for the term *hysteroscopy* were combined with the MeSH term *diagnosis*. The search was limited to human studies with no language restrictions. The authors and journal titles were removed from the retrieved citations, thereby blinding the reviewers (T.J.C. and D.V.). In addition, the Cochrane Library was searched. Reference lists of all known reviews and primary studies were checked, and manufacturers of hysteroscopes were contacted.

Selection Criteria

The review focused on observational studies in which the results of the diagnostic test of interest were compared with the results of a reference standard. The population of interest was women with abnormal premenopausal or postmenopausal uterine bleeding. The diagnostic test was hysteroscopy, and the diagnostic reference standard was endometrial histological findings. The verification of diagnosis following hysteroscopy was performed either at the same time (simultaneous) or after a short delay (sequential). The primary outcome measure was the accuracy with which endometrial cancer and hyperplasia were diagnosed. Secondary outcomes were failed procedures and major complications. The studies were identified by 2 reviewers independently (T.J.C. and D.V.). Final inclusion and exclusion decisions were made with reference to a checklist, which consisted of items based on the selection criteria. This checklist was piloted and the repeatability of its use was tested and confirmed. Disagreements about study inclusion and exclusion were initially resolved by consensus, and when this was not possible, they were resolved using arbitration by a third reviewer (K.S.K.). The agreement statistics among reviewers were computed.

Quality Assessment

All articles meeting the eligibility criteria were assessed for their methodologic quality, which involved scrutinizing study designs and the relevant features of population, test, and reference standard.[14-17] These features included the method of data collection and patient selection, description of the diagnostic test and histological reference standard, and presence of verification bias (completeness and timing of verification by reference standard) and blinding.[18] The following quality hierarchy of evidence in diagnostic test studies was also used[19]:

1. An independent, blind comparison with reference standard among an appropriate population of consecutive patients.
2. An independent, blind comparison with reference standard among an appropriate population of nonconsecutive patients or confined to a narrow population of study patients.
3. An independent, nonblind comparison with reference standard among an appropriate population of consecutive patients.
4. An independent, nonblind comparison with reference standard among an appropriate population of nonconsecutive patients or confined to a narrow population of study patients.
5. An independent, blind comparison among an appropriate population of patients, but reference standard not applied to all study patients.

Study levels 1 through 3 were considered to be of high quality and levels 4 and 5 were of low quality. We used a piloted checklist to identify and record items of study quality. The assessment of English-language articles was performed by 1 reviewer (T.J.C.) and foreign-language articles by 2 reviewers independently (T.J.C. and D.V.) following translation (when necessary). Any disagreement was resolved by consensus.

Data Abstraction

Three outcomes were considered: endometrial cancer, endometrial disease, and normal findings (functional or atrophic endometrium and benign focal abnormalities, eg, intrauterine polyps and fibroids). *Endometrial disease* was defined as including cancer, hyperplasia, or both, an approach that has been used in an earlier review of endometrial ultrasound.[20] We used this approach because endoscopic features of hyperplasia are not clearly distinct from those of endometrial cancer.[21,22] When cancer or hyperplasia were suspected within a focal abnormality, they were categorized as endometrial cancer and/or disease. Nonendometrial uterine malignancies were excluded from analysis.

Endometrial cancer was the primary outcome and data were abstracted as 2×2 tables of the hysteroscopy result (positive or negative for cancer) and the histological results (benign or malignant). Similarly, contingency tables were produced for hysteroscopy result and endometrial disease (benign or disease). To define test errors, cases in which the hysteroscopy result was normal and the reference standard result was abnormal were regarded as having false-negative results. False-positive results were cases in which the hysteroscopy result was abnormal and the reference standard result was normal.

Hysteroscopic procedures that failed to make a final diagnosis because of technical aspects (eg, cervical stenosis, anatomic factors, structural abnormalities), inadequate visualization (eg, obscured by bleeding, debris), or patient factors (eg, pain, intolerance) were categorized as failed procedures. Failure rates were recorded, but excluded from 2×2 tables. Information on menopausal status, the number of women recruited, and those whose outcome data were known was also sought from the articles. In addition, the setting (outpatient or inpatient) and technical details pertaining to the hysteroscopic examination were sought.

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Quantitative Data Synthesis

We calculated the true-positive rate (sensitivity), false-positive rate (1 – specificity), and likelihood ratios (LRs) for each study along with their 95% confidence intervals (CIs). When 2×2 tables contained 0 cells, 0.5 was added to each cell to enable our calculations.[23] Meta-analyses to produce summary pooled estimates of sensitivity and specificity were performed if these measures were found to be independent,[24,25] as indicated by lack of statistical correlation among them. However, estimates of sensitivity and specificity have limited value in clinical interpretation.[26-29] Therefore, we generated summary LRs as the principal measures of diagnostic accuracy based on the recommendations of the various evidence-based medicine groups.[26,28,30-33] The LRs indicate how much a given hysteroscopy finding increases or decreases the probability of having endometrial cancer or disease.[34] This is important in clinical decision making because the estimated probability of disease (or not having disease) is a prime factor in determining whether to withhold treatment, undertake further diagnostic testing, or treat without further testing.[35] Thus, the generation of LRs and posttest probabilities represents a more relevant method of establishing the utility of a test and reduces the risk of erroneous inferences being drawn.[27,36]

Heterogeneity of results among different studies was formally assessed graphically using sensitivity and specificity plots and the χ^2 test. To explore for clinical sources of heterogeneity, we defined the potential explanatory variables a priori.[37] In view of the potential influence of spectrum variability,[38,39] we considered menopausal status and setting to be important. In addition, we planned to examine the impact of study quality on estimation of accuracy according to individual quality items (patient selection, reference standard, completeness of verification, and blinding) and also according to an overall quality level (1-5) incorporating these items.[19]

We statistically examined estimation of accuracy in the subgroups. This was done by examining whether an explanatory variable affects the log of diagnostic odds ratio, a measure that accommodates LRs for both positive and negative test results, in a meta-regression analysis.[40,41] We initially performed univariable analyses followed by multivariable modeling, which controlled for confounding among variables.[41] The models produced by multivariable analysis included menopausal status (postmenopausal vs premenopausal and mixed population) and clinical setting (outpatient vs inpatient) as explanatory variables. The models were adjusted for the effect of study quality. For this we used quality as a binary variable (levels 1-3 vs levels 4-5), which avoided problems of colinearity among quality items. By testing only 3 variables in meta-regression analysis, we hoped to avoid spurious results due to "overfitting."[40] This approach is in keeping with published recommendations, which advocate a cautious examination of potential reasons for heterogeneity by specification of a small number of subgroup analyses in advance.[30,37,42]

If heterogeneity was encountered within subgroup meta-analysis, we initially pooled results from individual studies using both fixed-effects and random-effects models. In the presence of heterogeneity across studies, a random-effects model may be considered preferable[30,37,42,43] in meta-analysis, because this approach produces wider 95% CIs. However, this benefit has to be balanced against the potential disadvantage that by weighting smaller studies preferentially, it may produce biased point estimates of accuracy.[30] We examined for such a bias in our meta-analyses and reported results with a fixed-effects model, whereas a random-effects model was associated with higher estimates of accuracy. This allowed for a more conservative interpretation of the results. Furthermore, if heterogeneity remained within the prespecified clinical subgroups, we decided to base our inferences on high-quality studies (levels 1-3).

When certain variables were considered to be informative or were recommended by the peer reviewers, we conducted additional post hoc analyses to explore for causes of heterogeneity. Following univariable analyses, multivariable meta-regression analyses were performed to evaluate the effect of the explanatory variables on the log diagnostic odds ratio observed among individual studies.[41] The models produced by multivariable analysis included the following independent variables: description of test (adequate vs inadequate), complications (present vs absent), timing of verification (simultaneous vs sequential), method of data collection (prospective vs other), and completeness of follow-up (>90% vs <90%). However, the findings of these post-hoc analyses were considered in the context of hypothesis generation. We also explored for publication and related biases by producing a funnel plot of diagnostic odds ratios against corresponding SEs. The adjusted rank correlation method was used to test the correlation between estimated diagnostic odds ratios and their SEs.[44]

A sensitivity analysis was performed considering inadequate histological specimens, precluding a definitive diagnosis following the reference test, as negative results. This is because insufficient tissue samples are generally taken to mean absence of pathological findings.[45,46] We also excluded intrauterine polyps and fibroids as part of a sensitivity analysis to examine whether the presence of these focal lesions affected estimates of diagnostic accuracy.

RESULTS

A total of 65 primary studies (20 non–English-language studies), including 26 346 women, assessed the diagnostic accuracy of hysteroscopy in detecting serious endometrial disease and met the criteria for inclusion (FIGURE). Agreement regarding eligibility was 96% (weighted κ, 0.8). Postmenopausal women represented 29% of the populations studied. Details of the participants, interventions, outcomes, and study quality criteria of the studies selected for meta-analyses are summarized in TABLE 1. Of the 65 included

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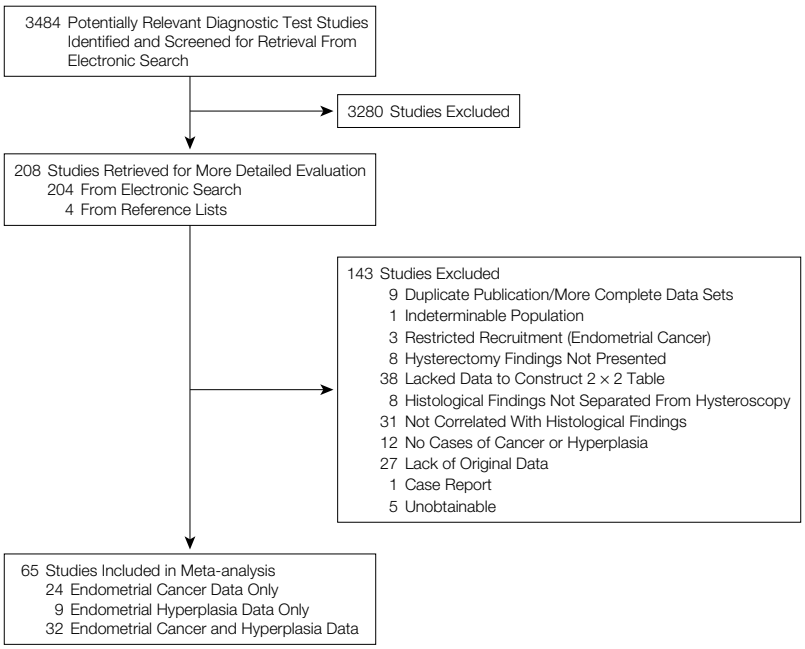
studies, 56 studies (24 649 women) assessed the diagnosis of endometrial cancer (TABLE 2). There was one study with the highest methodological quality (level 1); 1 was classified as level 2; 10 studies (15%) were level 3; 42 studies (65%) were level 4; and 11 studies (17%) were level 5.

Failure rates were clearly reported in 36 (55%) of the 65 studies. The overall failure rate was 937 (3.6%; 95% CI, 3.3%-3.8%) of 26 346 studies when considering all studies and 937 (4.9%; 95% CI, 4.6%-5.2%) of 19 323 studies when studies with unclear reporting were excluded. In those studies performed exclusively in one setting, the failure rate for an ambulatory procedure was 755 (4.2%; 95% CI, 3.9%-4.5%) of 18 126 studies compared with 86 (3.4%; 95% CI, 2.7%-4.2%) of 2526 studies for an inpatient procedure. However, the underlying reasons for failure varied among settings. Failed hysteroscopies in the outpatient setting resulted from technical problems (eg, cervical stenosis, anatomic factors, structural abnormalities) or patient factors (eg, pain, intolerance) more often than in inpatient setting (79% v 9%). By contrast, inadequate visualization (eg, obscured by bleeding, debris) was more common in the inpatient setting as a reason for failure (3% v 0.7%). Endometrial cancer was found in 8 (0.8%; 95% CI, 0.4%-1.7%) of 927 failed procedures reported in the 56 cancer studies, and endometrial disease was found in 25 (2.7%; 95% CI, 1.7%-3.9%) of 937 failed procedures reported in all included studies. In those studies in which data for postmenopausal women could be separated, the failure rate of 3.4% (95% CI, 2.7%-4.4%) for hysteroscopy was comparable with the overall rate (67 of 1948 women).

Eight cases of potentially serious complications (1 pelvic infection, 4 uterine perforations, 1 bladder perforation, 1 precipitation of a hypocalcemic crisis, and 1 anginal episode) were reported out of 25 409 successful procedures. However, ascertainment of serious complications may be suboptimal because only 19 (29%) of the 65 studies, which included 9413 successful procedures, explicitly stated the intention to report or actually reported complications.

Figure. Study Selection Process



Unobtainable indicates that manuscripts were not obtained despite electronic, local, national, and international library searches; and correspondence efforts with authors in relevant countries. The reference list for excluded studies is available from the corresponding author.

Endometrial Cancer

The variations in sensitivity were much greater than the variations in specificity, and there was no significant association between sensitivity and specificity (Spearman correlation coefficient $r = -0.06$; $P = .65$). Weighted by the number of cases, the overall sensitivity was 86.4% (95% CI, 84.0%-88.6%) and specificity was 99.2% (95% CI, 99.1%-99.3%) according to 56 studies of hysteroscopy for endometrial cancer. Because no association between sensitivity and specificity was found, a summary receiver operating characteristic curve was not generated.[25]

The pooled LRs for endometrial cancer are shown in Table 2. The pretest probability (prevalence) increased from 3.9% (95% CI, 3.7%-4.2%) to 71.8% (95% CI, 67.0%-76.6%) with a positive result and decreased to 0.6% (95% CI, 0.5%-0.8%) with a negative result. Heterogeneity of diagnostic performance among studies was present as confirmed by a statistically significant χ^2 test, and this remained within the prespecified clinical subgroups (setting and menopausal status). An explanation for heterogeneity was not provided by the study setting, menopausal status, or study quality (TABLE 3). The other potential explanatory variables defined post hoc also did not significantly influence diagnostic accuracy. The reported occurrence of complications was associated with reduced accuracy on univariable analysis, but this was not confirmed on multivariable analysis.

Endometrial Disease

As observed with endometrial cancer, the variation in sensitivity was much greater than the variation in specificity, and there was no significant association between sensitivity and specificity (correlation coefficient $r = 0.05$; $P = .70$). Diagnostic accuracy was lower for endometrial disease than endometrial cancer. The weighted overall sensitivity was 78.0%

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Table 1. Diagnostic Accuracy of Hysteroscopy in Detecting Endometrial Cancer and Hyperplasia in Women at Risk of Abnormal Endometrial Histology: Methodological Details[a]

Source	No. (%) of Women With Abnormal Uterine Bleeding				Study Quality Level	Reference Standard	Timing/ Completeness of Verification[c]	Follow-up, %
	Postmenopausal	Taking HRT	Premenopausal	Other[b]				
Alexopoulos et al,[47] 1999[d]	861 (33)	40 (2)	1647 (64)	33 (1)	5	Outpatient biopsy	Simultaneous/partial (49%)	>90
Altaras et al,[48] 1993[e]	39 (100)	NA	NA	NA	4	Outpatient biopsy	Simultaneous/ complete	>90
Azzena et al,[49] 1999[e]	9 (18)[f]	NA	11 (22)	30 (60)	2	Directed biopsy	Sequential/complete	>90
Bakour et al,[50] 1999[e]	35 (14)	77 (31)	136 (45)	NA	4	Dilation of the cervix and curettage of the endometrium; outpatient biopsy	Simultaneous/ complete	>90
Bocanera et al,[51] 1994[g]	72 (46)	NA	84 (54)	NA	5	Hysterectomy specimen; dilation of the cervix and curettage of the endometrium; outpatient biopsy	Sequential/complete[h]	<81
Buchholz et al,[52] 1988[i]	168 (100)	NA	NA	NA	4	Dilation of the cervix and curettage of the endometrium	Simultaneous/ complete	>90
Cacciatore et al,[53] 1994[e]	25 (56)	20 (44)	NA	NA	4	Dilation of the cervix and curettage of the endometrium	Simultaneous/ complete	>90
Cameron et al,[54] 2001[d]	12 (35)[f]	21 (65)	NA	NA	4	Hysterectomy specimen; outpatient biopsy	Sequential/complete	81-90
Caserta et al,[55] 1999[d]	NA	NA	NA	222 (100)	4	Directed biopsy	Simultaneous/ complete	>90
Dargent and Scasso,[56] 1984[d]	63 (33)	NA	143 (75)	NA	4	Outpatient biopsy	Simultaneous/ complete	>90
Davydov et al,[57] 1989[d]	46 (100)	NA	NA	NA	4	Dilation of the cervix and curettage of the endometrium	Simultaneous/ complete	>90
De Jong,[58] 1993[d]	62 (39)	NA	87 (54)	11 (7)	5	Dilation of the cervix and curettage of the endometrium; outpatient biopsy	Simultaneous/partial (74%)	>90
De Mendonca et al,[59] 1994[d]	158 (100)	NA	NA	NA	4	Not reported	Simultaneous/ complete	>90
De Silva et al,[60] 1997[j]	44 (88)	6 (12)	NA	NA	3	Hysterectomy specimen; dilation of the cervix and curettage of the endometrium	Sequential/complete	>90
De Vivo et al,[61] 1986[d]	NA	NA	18 (36)	32 (64)	4	Not reported	Not reported	>90
Decloedt and Fenton,[62] 1999[i]	NA	204 (30)	NA	469 (70)	4	Outpatient biopsy	Sequential/complete	>90
Descargues et al,[63] 2001[j]	8 (21)	1 (3)	29 (76)	NA	4	Directed biopsy; dilation of the cervix and curettage of the endometrium; outpatient biopsy	Simultaneous/ complete	>90
Elewa et al,[64] 2001[d]	20 (40)	NA	NA	30 (60)	4	Directed biopsy; dilation of the cervix and curettage of the endometrium	Simultaneous/ complete	>90
Epstein et al,[65] 2001[j]	77 (73)[k]	28 (27)	NA	NA	3	Hysterectomy specimen; directed biopsy; dilation of the cervix and curettage of the endometrium	Sequential/complete	>90
Gabrys et al,[66] 1994[d]	NA	NA	NA	63 (100)	4	Directed biopsy	Simultaneous/ complete	>90
Garuti et al,[67] 2001[l]	523 (34)[f]	NA	607 (41)	370 (25)	3	Hysterectomy specimen; directed biopsy; dilation of the cervix and curettage of the endometrium; outpatient biopsy	Sequential/complete	>90

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Table 1. Diagnostic Accuracy of Hysteroscopy in Detecting Endometrial Cancer and Hyperplasia in Women at Risk of Abnormal Endometrial Histology: Methodological Details[a] (cont)

Source	No. (%) of Women With Abnormal Uterine Bleeding				Study Quality Level	Reference Standard	Timing/ Completeness of Verification[c]	Follow-up, %
	Postmenopausal	Taking HRT	Premenopausal	Other[b]				
Gorostiaga et al,[68] 2001[j]	100 (100)	NA	NA	NA	3	Outpatient biopsy	Simultaneous/ complete	>90
Grozdanov,[69] 1988[d]	NA	NA	NA	631 (100)	4	Directed biopsy	Not reported/ complete	>90
Gucer et al,[70] 1996[d]	74 (72)	13 (13)	16 (15)	NA	4	Dilation of the cervix and curettage of the endometrium	Simultaneous/ complete	>90
Gupta et al,[71] 1996[e]	73 (100)	NA	NA	NA	4	Dilation of the cervix and curettage of the endometrium	Simultaneous/ complete	>90
Haller et al,[72] 1996[e]	81 (100)	NA	NA	NA	4	Dilation of the cervix and curettage of the endometrium	Simultaneous/ complete	>90
Iossa et al,[73] 1991[i]	NA	NA	NA	815 (100)	5	Dilation of the cervix and curettage of the endometrium; outpatient biopsy	Simultaneous/partial (37%)	>90
Itzkowic and Laverty,[74] 1990[g]	6 (12)	NA	43 (86)	1 (2)	3	Outpatient biopsy	Simultaneous/ complete	>90
Kovar et al,[75] 2000[i]	391 (36)[f]	206 (19)	495 (45)	NA	4	Dilation of the cervix and curettage of the endometrium	Simultaneous/ complete	>90
Krampl et al,[76] 2001[j]	5 (5)	6 (6)	89 (89)	NA	3	Directed biopsy	Simultaneous/ complete	>90
Kun et al,[77] 1999[j,k]	63 (20)	NA	180 (80)	NA	3	Dilation of the cervix and curettage of the endometrium; directed biopsy	Simultaneous/ complete	>90
La Sala et al,[78] 1987[d]	317 (33)	NA	415 (43)	244 (25)	5	Hysterectomy specimen; directed biopsy; outpatient biopsy	Sequential/partial (38%)	>90
Litta et al,[79] 1996[d]	251 (40)	NA	378 (60)	NA	4	Directed biopsy	Simultaneous/ complete	>90
Liu et al,[80] 1995[d]	130 (100)	NA	NA	NA	4	Not reported	Sequential/complete	>90
Lo and Yuen,[81] 2000[i]	503 (31)	NA	950 (59)	147 (10)	4	Directed biopsy; dilation of the cervix and curettage of the endometrium; outpatient biopsy	Simultaneous/partial (74%)	>90
Loverro et al,[82] 1996[d]	455 (46)	NA	525 (54)	NA	4	Directed biopsy; outpatient biopsy	Simultaneous/ complete	>90
Loverro et al,[83] 1999[e]	106 (100)	NA	NA	NA	4	Directed biopsy; outpatient biopsy	Simultaneous/ complete	>90
Luo and Chen,[84] 1989[d]	125 (100)	NA	NA	NA	4	Dilation of the cervix and curettage of the endometrium	Sequential/complete	>90
Madan and Al Jufairi,[85] 2001[i]	76 (13)	NA	480 (77)	64 (10)	4	Dilation of the cervix and curettage of the endometrium	Simultaneous/ complete	81-90
Maia et al,[86] 1996[d]	16 (34)	15 (32)	NA	16 (32)	4	Outpatient biopsy	Simultaneous/ complete	>90
Maia et al,[87] 1998[i]	NA	143 (100)	NA	NA	4	Hysterectomy specimen; directed biopsy; outpatient biopsy	Sequential/complete	>90
Mencaglia et al,[88] 1987[d]	NA	NA	NA	638 (100)[m]	5	Outpatient biopsy	Simultaneous/partial (33%)	>90
Nagele et al,[89] 1996[d]	202 (8)	NA	1925 (77)	373 (15)	5	Directed biopsy; outpatient biopsy	Simultaneous/partial (68%)	>90
Neis and Hepp,[90] 1986[e]	NA	NA	NA	307 (100)[m]	4	Dilation of the cervix and curettage of the endometrium	Sequential/complete	<81
Neumann and Astudillo,[91] 1994[d]	54	NA	31	NA	4	Dilation of the cervix and curettage of the endometrium	Simultaneous/ complete	>90

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Source	No. (%) of Women With Abnormal Uterine Bleeding				Study Quality Level	Reference Standard	Timing/ Completeness of Verification[c]	Follow-up, %
	Postmenopausal	Taking HRT	Premenopausal	Other[b]				
Ohad et al,[92] 1998[l]	173 (46)	NA	NA	200 (54)[m]	3	Dilation of the cervix and curettage of the endometrium	Simultaneous/ complete	>90
Okeahialam et al,[93] 2001[i]	NA	190 (100)	NA	NA	4	Directed biopsy; outpatient biopsy	Simultaneous/ complete	>90
Paschpoulos et al,[94] 1997[e]	NA	NA	NA	235 (73)[m]	4	Directed biopsy	Simultaneous/ complete	>90
Paya et al,[95] 1998[i]	866 (54)	109 (6)	641 (40)	NA	4	Not reported	Simultaneous/ complete	>90
Perez-Medina et al,[96] 1994[e]	80 (65)[f]	NA	53 (35)	NA	4	Dilation of the cervix and curettage of the endometrium; directed biopsy	Sequential/complete	>90
Possati et al,[97] 1994[d]	78 (78)	NA	NA	22 (22)	4	Not reported	Simultaneous/ complete	>90
Raju and Taylor,[98] 1986[d]	49 (70)	7 (10)	14 (20)	NA	4	Directed biopsy; dilation of the cervix and curettage of the endometrium	Simultaneous/ complete	>90
Salet-Lizee et al,[99] 1993[e]	43 (24)	32 (18)	103 (58)	NA	4	Dilation of the cervix and curettage of the endometrium	Simultaneous/ complete	>90
Sanfeliu et al,[100] 1990[i]	127 (26)	NA	482 (74)	NA	4	Outpatient biopsy	Unreported/complete	>90
Scwarzler et al,[101] 1998[g]	29 (30)	NA	69 (70)	NA	3	Dilation of the cervix and curettage of the endometrium	Simultaneous/ complete	>90
Sevcik et al,[102] 1998[d]	34 (47)	NA	NA	39 (53)	4	Directed biopsy; dilation of the cervix and curettage of the endometrium	Simultaneous/ complete	>90
Simon et al,[103] 1993[i]	15 (14)[f]	NA	NA	91 (86)	4	Hysterectomy specimen	Sequential/complete	<81
Sousa et al,[104] 2001[j]	75 (85)	13 (15)	NA	NA	1	Hysterectomy specimen; directed biopsy; outpatient biopsy	Sequential/complete	>90
Tahir et al,[105] 1999[j]	123 (31)	NA	277 (69)	NA	3	Dilation of the cervix and curettage of the endometrium; outpatient biopsy	Simultaneous/ complete	>90
Todorova et al,[106] 1998[e]	10 (50)	NA	10 (50)	NA	4	Not reported	Simultaneous/ complete	>90
Uhiara et al,[107] 1999[i]	61 (32)[f]	8 (5)	81 (43)	38 (20)	5	Outpatient biopsy	Simultaneous/partial (36%)	>90
Valli and Zupi,[108] 1995[e]	162 (17)[f]	NA	233 (25)	538 (58)	5	Directed biopsy	Simultaneous/partial (26%)	>90
Vercellini et al,[109] 1997[g]	NA	NA	793 (100)	NA	5	Outpatient biopsy	Simultaneous/partial (98%)	>90
Vigada and Malanetto,[110] 1995[d]	49 (58)	NA	23 (28)	12 (14)	4	Outpatient biopsy	Simultaneous/ complete	>90
Widrich et al,[111] 1995[e]	29 (22)	5 (4)	88 (68)	8 (6)	5	Outpatient biopsy; unspecified surgery	Sequential/partial (49%)	>90

[a] NA indicates data not available; HRT, hormone replacement therapy.
[b] Refers to the proportion of women included in the study who did not have abnormal uterine bleeding as an indication for hysteroscopy.
[c] Timing refers to when verification of diagnosis following hysteroscopy occurred. Simultaneous refers to diagnosis verification at the same time of hysteroscopy. Sequential indicates diagnosis verification occurred a short time after hysteroscopy.
[d] Data collection and patient selection information were not reported.
[e] Prospective study, but patient selection was not reported.
[f] Numbers calculated from initial proportion of patients within these groups before missing outcome data or duplicate testing was excluded.
[g] Data collection was not reported, but consecutive patient selection.
[h] Incomplete reporting of endometrial cancer (ie, not all histologically confirmed cases included in study analysis).
[i] Retrospective study, but patient selection was not reported.
[j] Prospective study with consecutive patient selection.
[k] All patients had endometrium thickness of greater than 5 mm on transvaginal ultrasound.
[l] Retrospective study with consecutive patient selection.
[m] Proportion of women included in the study in which the type of abnormal uterine bleeding was not specified.

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(95% CI, 76.3%-79.6%) and specificity was 95.8% (95% CI, 95.6%-96.1%). The summary LRs for endometrial disease are also shown in Table 2. The pretest probability increased from 10.6% (95% CI, 10.2%-11.0%) to 55.2% (95% CI, 52.4%-57.8%) with a positive result and decreased to 2.8% (95% CI, 2.4%-3.0%) with a negative result (Table 2).

There was heterogeneity in the overall and subgroup meta-analyses (Table 2). Clinical setting and menopausal status were significant explanatory variables for heterogeneity in univariable analyses as was the quality item of patient selection (Table 3). Poor study quality, the outpatient setting, and postmenopausal status were associated with significantly higher accuracy of hysteroscopy. The effect of these features on diagnostic accuracy was confirmed with multivariable analyses (Table 3). Of the variables defined post hoc, only follow-up of greater than 90% was associated with higher accuracy on both univariable and multivariable analyses (Table 3).

Sensitivity Analysis

In 12 studies (18%), it was not possible to determine the rate of inadequate specimens because of a lack of clear reporting, and the rate was assumed to be

Table 2. Diagnostic Accuracy of Hysteroscopy in Detecting Endometrial Cancer and Disease in Women With Abnormal Uterine Bleeding*

	No. of Data Points†	Likelihood Ratio (95% CI)		Posttest Probability (95% CI), %‡	
		Positive	Negative	Positive	Negative
Endometrial Cancer					
All studies	61	60.9 (51.2-72.5)	0.15 (0.13-0.18)	71.8 (67.0-76.6)	0.6 (0.5-0.8)
General study quality§					
High	11	34.8 (25.6-47.3)	0.21 (0.15-0.28)	58.6 (49.6-67.5)	0.8 (0.6-1.2)
Low	50	73.5 (59.5-90.8)	0.14 (0.12-0.17)	74.9 (69.6-79.9)	0.6 (0.5-0.7)
Outpatient setting	31	82.5 (64.9-105.0)	0.13 (0.10-0.16)	77.0 (71.4-82.2)	0.5 (0.4-0.7)
High quality	4	119.2 (63.0-225.7)	0.16 (0.11-0.24)	82.8 (70.7-90.8)	0.7 (0.4-1.0)
Low quality	27	76.5 (59.0-99.2)	0.12 (0.09-0.15)	75.6 (69.4-81.3)	0.5 (0.3-0.7)
Inpatient setting	16	21.9 (15.9-30.2)	0.28 (0.21-0.37)	47.1 (37.9-57.0)	1.1 (0.8-1.6)
High quality	5	8.6 (5.4-13.6)	0.36 (0.23-0.54)	25.8 (17.2-37.4)	1.4 (0.9-2.3)
Low quality	11	58.6 (33.5-102.7)	0.25 (0.17-0.35)	70.4 (56.3-81.8)	1.0 (0.7-1.5)
Postmenopausal women	16	38.3 (26.1-56.1)	0.13 (0.09-0.18)	60.9 (50.1-71.1)	0.5 (0.4-0.8)
High quality	2	45.4 (9.7-211.5)	0.09 (0.02-0.44)	64.8 (27.2-90.3)	0.4 (0.08-1.9)
Low quality	14	37.8 (25.5-56.0)	0.13 (0.09-0.19)	60.5 (49.5-71.1)	0.5 (0.3-0.8)
Premenopausal and postmenopausal women	45	72.5 (59.7-88.1)	0.16 (0.13-0.19)	74.6 (69.6-79.4)	0.6 (0.5-0.8)
High quality	9	34.0 (25.1-46.1)	0.22 (0.16-0.29)	58.0 (49.1-66.9)	0.9 (0.6-1.3)
Low quality	36	104.7 (80.7-135.9)	0.14 (0.12-0.18)	81.0 (75.6-85.6)	0.6 (0.5-0.7)
Endometrial Disease					
All studies	71	10.4 (9.7-11.1)	0.24 (0.22-0.25)	55.2 (52.4-57.8)	2.8 (2.4-3.0)
General study quality§					
High	12	5.5 (4.8-6.3)	0.31 (0.27-0.37)	39.4 (35.3-43.8)	3.5 (3.0-4.4)
Low	59	12.6 (11.5-13.7)	0.22 (0.1-0.24)	59.9 (56.6-62.3)	2.5 (1.1-2.9)
Outpatient setting	36	13.9 (12.6-15.3)	0.21 (0.19-0.23)	62.2 (58.9-65.4)	2.4 (2.1-2.8)
High quality	4	8.3 (6.9-10.1)	0.29 (0.24-0.35)	49.6 (43.9-55.5)	3.3 (2.7-4.2)
Low quality	32	16.2 (14.5-18.2)	0.20 (0.17-0.22)	65.7 (62.2-69.2)	2.3 (1.9-2.7)
Inpatient setting	18	4.6 (4.0-5.3)	0.39 (0.34-0.44)	35.3 (31.2-39.6)	4.4 (3.7-5.2)
High quality	5	2.4 (2.0-2.9)	0.45 (0.34-0.59)	22.1 (18.5-26.4)	5.1 (3.7-6.8)
Low quality	13	7.0 (5.6-8.6)	0.37 (0.32-0.43)	45.4 (38.9-51.5)	4.2 (3.5-5.1)
Postmenopausal women	18	20.4 (15.7-26.6)	0.14 (0.11-0.19)	70.8 (64.1-76.7)	1.6 (1.2-2.3)
High quality	2	71.5 (9.8-522.9)	0.09 (0.02-0.41)	89.5 (52.7-98.5)	1.1 (0.2-4.8)
Low quality	16	19.6 (15.0-25.6)	0.15 (0.11-0.19)	69.9 (63.0-76.0)	1.8 (1.2-2.3)
Premenopausal and postmenopausal women	53	9.6 (9.0-10.4)	0.25 (0.23-0.27)	53.2 (50.1-56.2)	2.9 (2.6-3.2)
High quality	10	5.2 (4.6-6.0)	0.28 (0.23-0.34)	38.1 (34.3-42.6)	3.2 (2.6-4.0)
Low quality	43	11.8 (10.8-12.9)	0.20 (0.18-0.22)	58.3 (55.1-61.5)	2.3 (2.0-2.7)

*An estimate of the pretest probability was obtained by calculating the prevalence of the outcome event in the overall population in the 65 included studies. The following equation was used for calculating posttest probability: likelihood ratio × pretest probability/[1 − pretest probability × (1 − likelihood ratio)]. The pretest probability was 3.9% (95% confidence interval [CI], 3.7%-4.2%) for endometrial cancer and 10.6% (95% CI, 10.2%-11.0%) for endometrial disease.

†There are 61 data points presented in 56 studies of endometrial cancer and 71 data points presented in the 65 studies of endometrial disease. In some studies, data could be extracted for both postmenopausal and premenopausal women, so there are more data points than studies. Data could not be split by setting or menopausal status for all studies.

‡The 95% CIs for posttest probability were calculated by using lower and upper limits of 95% CIs of pretest probabilities and likelihood ratios.

§High-quality studies were levels 1 through 3 and low-quality studies were levels 4 and 5.

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0 for the purpose of analysis. This gave an inadequate specimen rate on the reference test of 1196 (4.7%; 95% CI, 4.5%-5.0%) of 25 409 specimens. The pooled LRs were not altered if inadequate samples were regarded as negative results. There were 4622 focal lesions (intrauterine polyps or fibroids) detected in 25 409 hysteroscopies (prevalence, 18%) reported in 55 of the 65 primary studies. In 152 of the 4622 focal anomalies (prevalence, 3%), endometrial cancer (17 cases) or hyperplasia (135 cases) was present. Estimates of accuracy for endometrial cancer were not affected when focal abnormalities were excluded as part of a sensitivity analysis (LR, 59.3 [95% CI, 49.2-71.6] for positive and LR, 0.14 [95% CI, 0.12-0.16] for negative test results). There was a trend toward reduced accuracy for endometrial disease when focal abnormalities were excluded, although the magnitude of this reduction was small (LR, 8.4 [95% CI, 7.8-9.0] for positive and LR, 0.18 [95% CI, 0.16-0.20] for negative test results).

Statistical tests (rank correlation) to explore for publication and related biases found that funnel plot asymmetry was not statistically significant ($P = .34$ for endometrial cancer and $P = .12$ for endometrial disease).

Table 3. Exploration of Heterogeneity in Estimation of Accuracy of Hysteroscopy for Diagnosis of Endometrial Cancer and Disease*

	Univariable Analysis		Multivariable Analysis: Hypothesis Testing		Multivariable Analysis: Hypothesis Generating	
Heterogeneity Outcome	Coefficient (SE)†	*P* Value	Coefficient (SE)†	*P* Value	Coefficient (SE)†	*P* Value
Endometrial Cancer						
Clinical features‡						
Setting: outpatient vs inpatient	0.60 (0.44)	.18	0.52 (0.47)	.26	0.89 (0.51)	.09
Menopausal status: postmenopausal vs mixed	−0.64 (0.69)	.36	−0.41 (0.72)	.57	−0.55 (0.75)	.47
Study quality‡						
Patient selection: consecutive vs nonconsecutive	−0.08 (0.46)	.86	NA	NA	NA	NA
Reference standard: outpatient biopsy vs other	0.45 (0.61)	.46	NA	NA	NA	NA
Complete verification: present vs absent	−0.14 (0.47)	.77	NA	NA	NA	NA
Blinding: blind vs not blind	−0.39 (2.1)	.85	NA	NA	NA	NA
Quality level of study: 1-3 vs 4-5§	−0.18 (0.52)	.73	−0.12 (0.52)	.82	−0.35 (0.70)	.62
Hysteroscopic procedure‖						
Description of diagnostic test: adequate vs inadequate	−1.11 (0.57)	.06	NA	NA	−1.02 (0.77)	.19
Complications: present vs absent	−1.71 (0.67)	.01	NA	NA	−1.28 (0.87)	.15
Study quality items‖						
Timing of verification: sequential vs simultaneous	0.13 (0.48)	.78	NA	NA	0.07 (0.66)	.91
Data collection: prospective vs other	−0.36 (0.55)	.52	NA	NA	0.01 (0.60)	.99
Follow-up: >90% vs <90%	−0.28 (0.99)	.98	NA	NA	0.35 (1.03)	.73
Endometrial Disease						
Clinical features‡						
Setting: outpatient vs inpatient	1.18 (0.37)	.002	1.25 (0.33)	.001	0.54 (0.38)	.15
Menopausal status: postmenopausal vs mixed	1.41 (0.69)	.045	1.54 (0.60)	.01	1.05 (0.56)	.06
Study quality‡						
Patient selection: consecutive vs nonconsecutive	−1.08 (0.38)	.005	NA	NA	NA	NA
Reference standard: outpatient biopsy vs other	0.36 (0.50)	.48	NA	NA	NA	NA
Complete verification: present vs absent	0.57 (0.46)	.22	NA	NA	NA	NA
Blinding: blind vs not blind	1.81 (2.77)	.52	NA	NA	NA	NA
Quality level of study: 1-3 vs 4-5§	−1.10 (0.41)	.009	−1.28 (0.37)	.001	−1.69 (0.60)	.006
Hysteroscopic procedure‖						
Description of diagnostic test: adequate vs inadequate	1.61 (0.82)	.05	NA	NA	1.22 (0.73)	.10
Complications: present vs absent	−2.12 (0.64)	.001	NA	NA	−1.15 (0.73)	.12
Study quality items‖						
Timing of verification: sequential vs simultaneous	0.002 (0.43)	>.99	NA	NA	0.88 (0.57)	.13
Data collection: prospective vs other	0.82 (0.52)	.12	NA	NA	0.58 (0.43)	.19
Follow-up: >90% vs <90%	1.59 (0.53)	.004	NA	NA	1.78 (0.52)	.001

*Results are based on data from 61 data points presented in the 56 studies of endometrial cancer and 71 data points presented in the 65 studies of endometrial disease. In some studies, data could be extracted for both postmenopausal and premenopausal women; thus, there are more data points than studies. NA indicates there is no value available because outcome was not included in multivariable analyses.

†The dependent variable is the log diagnostic odds ratio; a positive coefficient means that the diagnostic accuracy as measured by the odds ratio is increased and a negative coefficient means that it is reduced in relation to the variable. $P < .05$ is considered statistically significant.

‡Defined a priori.

§Quality levels were on a scale from 1 to 5.[19]

‖Defined post hoc.

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COMMENT

Our review shows that diagnostic hysteroscopy is safe, with a low incidence of serious complications and a small failure rate. When the uterine cavity is adequately visualized, hysteroscopy is highly accurate and thereby clinically useful in the diagnosis of endometrial cancer. Moreover, performance of the test does not appear to be significantly altered by the clinical setting or menopausal status.

In view of the lack of satisfactory explanations for heterogeneity among studies, it may be reasonable to base inferences on the overall pooled result for the hysteroscopic diagnosis of endometrial cancer.[112] Because the diagnosis of endometrial cancer is important, the high LR of 60.9 (95% CI, 51.2-72.5) for a positive test result on hysteroscopy should increase most pretest probabilities over any threshold for advanced management.[35] The pretest probability (or prevalence) of cancer in our review of women with abnormal uterine bleeding was 4%, but was higher at 11% in postmenopausal women, which is consistent with the published literature.[8] In contrast, the LR of 0.15 (95% CI, 0.13-0.18) for a negative test result is not low enough to negate the need for further diagnostic testing, thereby reducing the utility of hysteroscopy in isolation for exclusion of diagnosis. Hysteroscopy is thus highly accurate and thereby clinically useful in diagnosing endometrial cancer in women with abnormal uterine bleeding. However, its high accuracy relates to diagnosing cancer rather than excluding it.

The diagnostic accuracy of hysteroscopy in endometrial disease is more modest so that it cannot be diagnosed or excluded with a high level of certainty and further testing will be indicated. In contrast to endometrial cancer, hysteroscopy is more accurate for the diagnosis of endometrial disease in postmenopausal women and when undertaken in the outpatient setting. In our review, statistically significant differences between these clinical subgroups are quantitative rather than qualitative. Invariably such differences explain only part of the heterogeneity. Therefore, it may be argued that the overall average estimates may provide the best summary of the available evidence.[112] However, cautious interpretation would demand that we consider the test's performance to vary according to setting and menopausal status. Therefore, our inferences are based on these clinical subgroups and methodological quality in the case of endometrial disease.

The strength of our overview is based on its compliance with criteria for performing a rigorous systematic review.[14,24,113,114] These included, among others, the use of study quality assessment[15,115] and investigation for possible sources of heterogeneity planned a priori. However, our review could be criticized for 2 main reasons. The first reason relates to the differences in results among individual studies included in the review. Homogeneity of results from study to study is one of the criteria for meta-analysis, but presence of inconsistency itself does not always invalidate a meta-analysis. In this situation, it is important to consider possible reasons for heterogeneity. We explored the sources of heterogeneity as thoroughly as possible in accordance with published guidelines,[30,42,43] taking into account differences in methodological quality and study characteristics, using both univariable and multivariable analytic techniques. However, these analyses are often restricted due to the number of available studies. Although our review included numerous studies, the exploration of underlying sources of heterogeneity may be limited without access to individual patient data.[116]

The second area for possible criticism relates to potential bias due to variation in histological reference standard and lack of blinding in its assessment. Hysterectomy specimens are regarded as the criterion standard for verification of endometrial disease, but the exclusive use of this reference standard in a diagnostic test study is not feasible. Therefore, it is not surprising that many studies included in our review obtained endometrial tissue using other methods. Bias due to misdiagnosis by these methods is, however, unlikely to be a significant problem. This is because outpatient endometrial sampling methods are considered to be highly accurate for endometrial cancer and of reasonable, although more modest, accuracy in endometrial hyperplasia.[19,117] Blinding in this overview may be less important than in other diagnostic test studies. This is because the histological diagnosis of endometrial cancer, the primary outcome measure, is an objective one[118] and consequently not as susceptible to expectation bias. Moreover, both subgroup and meta-regression analyses did not show the type of reference standard or blinding to be significant predictors for diagnostic performance.

This quantitative review provides precise estimates of accuracy of hysteroscopy in the diagnosis of serious endometrial disease (cancer and hyperplasia). Our results indicate that hysteroscopy is highly accurate and thereby clinically useful in diagnosing endometrial cancer in women with abnormal uterine bleeding, and it is moderately useful in diagnosing endometrial disease. In addition to hysteroscopy, other new diagnostic modalities, namely, transvaginal ultrasonography and endometrial biopsy, have been introduced to replace traditional inpatient dilation of the cervix and curettage of the endometrium.[119] There remains a considerable debate regarding the best sequence and combination of these new tests for evaluating women with abnormal uterine bleeding.[5,10,120-126] Our review provides information on accuracy of hysteroscopy. The findings of our review can be used to compare hysteroscopy with other tests in the diagnosis of serious endometrial disease.

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Acquisition of data: Clark, Voit, Hyde, Khan.
Analysis and interpretation of data: Clark, Gupta, Song, Khan.
Drafting of the manuscript: Clark, Khan.
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Statistical expertise: Clark, Song, Khan.
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Study supervision: Gupta, Song, Khan.

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