Is the ThinPrep better than conventional Pap smear at detecting cervical cancer?

EVIDENCE-BASED ANSWER

Conclusions regarding the ThinPrep are difficult to make due to the complexity of cervical cancer screening and the lack of adequate outcome-based data. However, current evidence supports the following: the ThinPrep is more sensitive than the conventional Papanicolaou (Pap) smear at detecting cervical cancer (strength of recommendation [SOR]: **A–**, based on 1 large validating cohort study with a good reference standard and 1 systematic review). There is insufficient evidence to recommend 1 preparation over the other (SOR: **B–**, based on several systematic reviews that include studies with poor reference standards).

The ThinPrep is a cost-effective screening tool if used at 3-year intervals (SOR: **B**, based on 1 systematic review and a decision analysis model). Additional advantages of the ThinPrep include being able to perform human papillomavirus (HPV) testing on the liquid. This is the preferred triage strategy for atypical squamous cells of undetermined significance (ASCUS) Pap smears (SOR: **A**, based on a large randomized, controlled trial).

EVIDENCE SUMMARY

The conventional Pap smear is the standard screening test for cervical neoplasia. Despite success, the Pap smear has high false-negative rates due to poor sensitivity (51%; 95% confidence interval [CI], 37%–66%).[1] The ThinPrep was developed to improve sensitivity by providing a monolayer of cells to the cytologist for review. A population-based comparative analysis of good quality shows that the new technology is better at detecting cancer precursors, but other systematic reviews that include less rigorous studies can only suggest it.

The overwhelming problem with most studies is they lack adequate reference standards. Customary criteria for evaluating diagnostic tests require that a "gold standard" reference be used, and that both the abnormal and normal results are validated against it. For cervical cancer screening, the "gold standard" is histology.

Only 1 analysis met the standard criteria. This prospective, population-based study of 8636 women reported that the ThinPrep was significantly more sensitive than the conventional smears at detecting high-grade squamous intraepithelial lesions (HSIL) and cancer, with sensitivity rates of 92.9% and 100% vs 77.8% and 90.9%, respectively ($P<.001$).[2] This evidence demonstrates that the ThinPrep is better at detecting cervical cancer.

Several systematic reviews summarize the many studies that compare ThinPrep with the conventional Pap. Unfortunately, conclusions are difficult to interpret. A recent quantitative review implies that the ThinPrep increases cytologic diagnoses of cervical cancer and its precursors.[3] A strength of this review is the inclusion of 10 articles with histology as the reference standard. The data from 21,752 patients compared the sensitivity and specificity rates of Thin Prep with conventional Pap for detecting abnormal histology. Sensitivity rates were reported as 76% (ThinPrep) and 68% (conventional), but the differences met statistical significance in only 2 of the included studies. Similarly, the overall specificity rates of the ThinPrep vs conventional Pap was 86% vs 79%, and again the differences did not usually reach statistical significance. The authors hypothesize that widespread use of ThinPrep could potentially detect an additional 162,000 patients with HSIL and 3000 patients with invasive cervical carcinoma.

A large meta-analysis of 25 prospective studies including over 500,000 women reported that ThinPrep increased detection of low-grade squamous intraepithelial lesions (LSIL) (odds ratio [OR]=2.15; 95% CI, 2.05–2.26) and HSIL (OR=2.26; 95% CI, 1.53–1.76), but the conclusions were severely limited by lack of a reference standard and high heterogeneity between study

Advantages of the ThinPrep include being able to perform HPV testing on the liquid

populations.[4] Another review found insufficient evidence to even judge the new test.[5]

A large evidence review done for the Agency for Healthcare Research and Quality (AHRQ) concluded that the quality of the available literature is poor. Two of the 3 trials reviewed had major methodological flaws that prevented an appropriate comparison of the data to show a modestly higher sensitivity of the ThinPrep.[1] From these reviews, we cannot recommend one technique over the other.

When evaluating a new screening test, cost is important. The AHRQ review[1] and a modeled cost and outcomes analysis[6] concluded that liquid-based cytology falls within the accepted ranges of cost-effectiveness if used at 3-year screening intervals. Another computer-based model evaluated different triage strategies for ASCUS Pap smears and found that reflex HPV testing provides the same or greater life expectancy benefits and is more cost-effective.[7] This strategy requires the use of liquid-based cytology. The large ALTS trial supports the use of liquid-based cytology because it has shown HPV testing in patients with ASCUS decreases the need for colposcopy.[8] Ultimately, when deciding which Pap test is better, many things in addition to sensitivity must be considered.

RECOMMENDATIONS FROM OTHERS

The US Preventive Services Task Force concludes that the evidence is insufficient to recommend for or against the routine use of new technologies to screen for cervical cancer. They acknowledge that ThinPrep may have improved sensitivity over conventional Pap smears but may possibly have lower specificity. The Task Force notes that ThinPrep could be cost-effective with longer screening intervals and can be helpful for the management of ASCUS.[9]

No current screening guidelines specifically recommend newer Pap test technologies in favor of conventional Pap tests. These associations include American Cancer Society, American Academy of Family Physicians, American College of Preventive Medicine, and American College of Gynecology.

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CLINICAL COMMENTARY

ThinPrep's high sensitivity and viral typing may be advantageous in some cases

Because the ThinPrep is expensive and not endorsed by major medical policy groups, it is not time for family physicians to switch to the ThinPrep en masse. However, I think 2 groups will be looking carefully at this technology.

First, in settings where annual follow-up is unreliable or impractical, the ThinPrep's high sensitivity will definitely be advantageous. Second, physicians who want to use HPV-based colposcopy guidelines will appreciate the ThinPrep's viral typing capabilities, although the unresolved issue of screening frequency will remain a problem. Advertising pressures, advocacy groups, and payer response will also shape this ongoing discussion.

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Does treatment of acne with Retin A and tetracycline cause adverse effects?

EVIDENCE-BASED ANSWER

Adverse reactions to long-term tetracycline therapy are rare, and most will occur within 2 months of initiating therapy (strength of recommendation [SOR]: **B**, systematic review of ecological studies). Rare but serious drug reactions include a severe cutaneous reaction, hypersensitivity syndrome reaction, serum sickness–like reaction, and isolated single-organ dysfunction (SOR: **B**, systematic review).

Duration of antibiotic treatment is strongly associated with increased bacterial resistance (SOR: **B**, systematic review and 1 outcomes study), but antibiotics for acne do not appear to interfere with oral contraceptive efficacy (SOR: **B**, case-control study and supporting expert opinion). Laboratory monitoring is not indicated in otherwise healthy patients (SOR: **B**, consistent cohort studies).

No reports have been published regarding long-term topical tretinoin (Retin A) therapy. Short-term follow-up reports note no systemic effects (SOR: **C**, expert opinion), no teratogenicity (SOR: **B**, single case control study), and negligible systemic absorption (SOR: **B**, outcome studies). Thus, long-term topical tretinoin is presumed to be safe (SOR: **C**, expert opinion and extrapolation of pharmacologic data).

EVIDENCE SUMMARY

Tetracycline

A study of the safety of tetracycline,[1] which used reports in a drug safety database and a literature review of reported adverse events, concluded that rare but serious events do occur with tetracycline. Severe cutaneous adverse reaction was the most common reported single-organ dysfunction. Other rare events included hypersensitivity syndrome reactions and serum sickness–like reactions.

Since baseline rates of tetracycline use are unknown, it is impossible to ascertain the event rates for these rare reactions. Most of these serious adverse events occur less than 2 months after initiating therapy; they typically include general symptoms such as fever, malaise, and arthralgias, but may also include major organ involvement. The study suggested no clear treatment for these complications, but recommended discontinuing tetracycline and avoiding the entire tetracycline class of drugs.[1] No evidence supports previous concerns that tetracycline causes drug-induced lupus.

A systematic review confirms that treating acne with long-term systemic antibiotics leads to increased antimicrobial resistance.[2,3] A well-designed cohort trial showed that *Propioni-bacterium acnes* resistance was directly related to duration of antibiotic therapy.[4] This is clinically important because resistance levels correlate with therapeutic failure.[2] Rotating antibiotics on a long-term basis actually increases bacterial resistance patterns and can exacerbate the problems of increasing resistance and poor treatment outcomes.[2]

A relatively large retrospective cohort study of oral contraceptive users in a dermatological practice showed no difference in contraceptive failure rates between those prescribed common antibiotics (including tetracycline) and controls (1.6% vs 0.96%; 95% confidence interval [CI] for the difference, 0.81–2.1).[5]

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