



Quest
Diagnostics

NEWS

Editor's Note:

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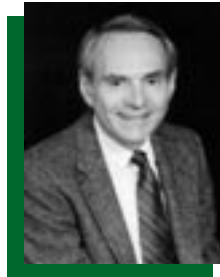
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**QUEST
DIAGNOSTICS'
VALUES**

- *Quality*
- *Integrity*
- *Innovation*
- *Accountability*
- *Collaboration*
- *Leadership*

TAKE IT OFF

Today, the U.S. population lives in a highly toxic health environment characterized by a highly sedentary life-style aggravated by a diet overly rich in fats and refined sugar. One of the consequences of this metabolically toxic milieu, in which many of us choose to live, is an epidemic of obesity, characterized by an increase in visceral adipose tissue.



The principal metabolic complications of this epidemic, with its easily recognizable central adiposity, are dyslipidemia and hyperinsulinemia, with resultant increased rates of cardiovascular disease, diabetes and hypertension. According to the Centers for Disease Control and Prevention, obesity among adults rose 61% in the last decade. Obesity and overweight in adulthood are associated with large decreases in life expectancy and increases in early mortality. These decreases are similar to those seen with smoking.

Adipose tissue is now recognized as an endocrine organ that secretes hormone and cytokine mediators of inflammation and lipogenesis. Elsewhere in this issue we discuss high-sensitivity C-reactive protein, or Cardio CRP (CCRP). A product of inflammatory cytokines, CCRP is a novel atherosclerosis risk factor or marker—its exact role is yet to be elu-

cidated. Prospective and retrospective studies have confirmed CCRP as a risk marker beyond the traditional lipid risk markers such as low-density lipoprotein (LDL) cholesterol.

Also, it has been demonstrated that CCRP levels, correlated with visceral adipose tissue area and waist circumference, are markers of visceral adiposity. The greater the adipose tissue areas and the greater the waist circumference, the higher the level of CCRP. Tissue plasminogen activator inhibitor-1 (PAI-1), an inhibitor of fibrinolysis and an additional cardiovascular disease (CVD) risk factor, is secreted by adipose tissue. In a study of overweight and obese diabetic and nondiabetic women, visceral fat was noted as the most important determining factor for PAI-1 activity, even after adjusting for insulin and lipid levels.

So what to do about this epidemic that is threatening the health of our nation? The short answer is to educate and work with patients to embrace a healthy life-style and lose an appropriate amount of weight. Any physician or patient who has tried to do this can tell you that it is much easier said than done.

If drug therapy is considered necessary, available medication can induce a feeling of satiety or block intestinal absorption of fat. Clinical

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BEST

WHAT IS THE BEST TEST TO ASSESS PAP TEST SPECIMEN ADEQUACY?

TEST

The Bethesda System (TBS) terminology for reporting results of cervical cytology made substantial changes in specimen adequacy terminology and categorization. (See summer 2002 News article.)

Editor's Note: Recall that TBS 2001 has only two adequacy categories—Satisfactory for Evaluation and Unsatisfactory. The previous Satisfactory But Limited By ... category (SBLB) was eliminated.

The participants of the Bethesda conference were concerned that the changes might lead to confusion concerning optimal patient management based on specimen adequacy. Prior to publication of TBS 2001, the American Society for Colposcopy and Cervical Pathology (ASCCP) practice guidelines addressed issues related to Pap smear quality based on TBS 1991. There were no truly evidence-based guidelines addressing the screening of women whose Pap test lacked a transformation zone component or demonstrated partially obscuring blood or inflammation.

The rationale for elimination of the SBLB category was that it was confusing to many clinicians. Some described it as an oxymoron—was it satisfactory or limited? This was compounded by the fact that there was conflicting data regarding the necessity for an earlier than routine repeat of the Pap test. This uncertainty led to controversies in patient care, risk management strategies and

third party payer reimbursement for follow-up Pap testing.

The ASCCP agreed to address these concerns by convening a task force to establish Pap test specimen adequacy management guidelines. Unfortunately, the topic was not introduced in time to reach an agreement during the ASCCP meeting held to develop the consensus guidelines for the management of cervical cytologic abnormalities and cervical cancer precursors.

A task force composed of TBS 2001 forum members and ASCCP members met several times to develop guidelines based on extensive literature review and the expert opinion of panel members. Draft guidelines were submitted to the ASCCP steering committee and various other experts for comment and modification.

The following three issues were addressed:

Issue 1. *What is the recommended follow-up for women with a negative (for intraepithelial lesion or malignancy) Pap test lacking an endocervical/transformation zone component?*

The preferred management recommendation for most women undergoing a routine annual/biennial screening is a repeat Pap test in 12 months. An early repeat (within 6 months) may be beneficial for women who satisfy the following conditions:

- a previous Pap test interpreted as a

squamous abnormality (ASC-US, or worse);

- a previous Pap test interpreted as a glandular abnormality;
- a positive test for high-risk human papilloma virus DNA within the previous 12 months;
- clinician inability to clearly visualize the cervix or sample the endocervical canal;
- immunosuppression;
- insufficient previous screening (not participating in at least a biennial Pap test screening); and
- a postpartum repeat preferred for pregnant patients.

Issue 2. *What is the recommended follow-up for women with a negative (for intraepithelial lesion or malignancy) Pap test that has partially obscuring blood, inflammation, other partially obscuring factors, or partial air-drying?*

The preferred management recommendation for most women undergoing a routine annual/biennial screening is a repeat Pap test in 12 months. An early repeat (within 6 months) may be beneficial for women who satisfy the following conditions:

- a previous Pap test interpreted as a squamous abnormality (ASC-US, or worse);
- a previous Pap test interpreted as a glandular abnormality;
- a positive test for high-risk human

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HERPES SIMPLEX ANTIBODY TESTING — WHY AND WHEN?

Using new and more accurate antibody tests, we now know that by age 30 almost 25% of Americans have detectable herpes simplex virus 2 (HSV-2) antibodies. That represents about 50,000,000 persons who are infected with HSV-2. Of the 25% of infected individuals, only 10-20% (2-5% of the total) have a history of a classical herpes simplex virus (HSV) infection. Another 10-20% of the total will have totally asymptomatic disease, and an astounding 60-80% will have unapparent or unrecognized genital HSV-2 infection. These patients have “atypical” symptoms and are not usually diagnosed as having genital HSV infection.

The manifestations of atypical urogenital HSV infection are too varied to completely cover in this publication, but they include dysuria, lower back pain, aching lower limbs, reddening of buttocks and thighs, vaginal/urethral discharge, etc. Most infections are due to sexual transmission from infected individuals who do not have the classic genital lesions. Clinicians are familiar

with the classic presentation of painful disabling HSV type 1 (HSV-1) or type 2 genital infections. Patients with genital HSV-1 infection have significantly fewer outbreaks than those with HSV-2, and shed virus less frequently.

There are at least two other types of presentation—the unrecognized or unapparent infection and subclinical HSV shedding. In the latter form, patients have virus that is retrievable from mucocutaneous surfaces without any clinical manifestations of disease. Greater than 90% of persons infected with genital HSV-2 shed virus asymptotically at some time following primary infection. Within the first few years of being infected, most people are shedding virus at least 10% and 20% of days between outbreaks. Some individuals shed considerably more than that.

Genital HSV infection causes a great deal of physical and emotional distress especially in regard to personal relationships. The importance of accurate HSV antibody testing cannot be overemphasized. Benefits of test-

ing are as follows:

- provide the basis for proper and informed clinical management of HSV infection;
- ensure timely and appropriate treatment; and
- allow counseling on specific disease type and risk factors for disease transmission.

Culture is usually considered the “gold standard” for confirming the diagnosis of an infectious disease. A positive culture is useful; however, a negative culture does not exclude disease. Viral culture often requires the presence of a significant number of viable organisms to allow detection. The sensitivity of HSV culture declines rapidly—usually within the first several days after lesions appear. In addition, pre-analytic variables such as transport temperature, transport medium, and time between sample collection and culture inoculation can contribute to a false-negative result.

The FDA has recently approved

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SHOULD WE MEASURE BOTH CCRP AND LDL?

Almost one half of patients who suffer a heart attack have normal serum lipids. Obviously, there must be risk factors for cardiovascular disease (CVD) other than dyslipidemia. Low-density lipoprotein (LDL) cholesterol is a therapeutic target used by physicians to manage patients who have elevated total and LDL cholesterol levels. What about those patients with normal or minimally abnormal serum lipids who are also at risk for CVD?

A recent study published in the *New England Journal of Medicine* measured high-sensitivity C-reactive protein—also known as Quest Diagnostics as Cardio CRP (CCRP)—in over 27,000 healthy women. The study group was followed for a mean

of eight years looking for the occurrence of myocardial infarction, ischemic stroke, coronary revascularization, or death from CVD.

After adjustment for age, smoking status, diabetes, blood pressure and hormone-replacement therapy, the relative risks (compared to lowest risk) of first CVD events according to increasing quintiles of CCRP were 1.4, 1.6, 2.0 and 2.3 ($P < 0.001$). The corresponding relative risks in increasing quintiles of LDL cholesterol were 0.9, 1.1, 1.3 and 1.5 ($P < 0.001$). Overall, 77% of all CVD events occurred in women with LDL cholesterol levels below 160 mg/dL, and 46% occurred in women with LDL cholesterol levels less than 130 mg/dL.

The authors state that because

CCRP and LDL cholesterol measurements tended to identify different high-risk groups, screening for both markers provided better prognostic information than screening for either alone. Independent effects also were noted for CCRP in analyses adjusted for all components of the Framingham risk score.

Editor's Note: This paper sparked a great deal of discussion at the recent national meeting of the American Heart Association (AHA) and was widely reported in the lay press. The long-awaited CDC and AHA consensus panel report on the use of CCRP in practice is scheduled for release in the first quarter of 2003.

Stay tuned! (*NEJM* 2002; **347**:1557-1565, 1615-1616)

TAKE IT OFF

(Continued from page 1)

trials have shown that the anticonvulsant drug, Topiramate, can produce a significant weight loss in obese patients over a period of at least 6 months. These agents can be part of a sensible weight loss program, combining initial medication with sustainable behavior modification. The bottom line is that many Americans need to take it off and keep it off. (Notes from a symposium held in conjunction with the American Diabetes Association's 62nd Annual Meeting, *Management of Type 2 Diabetes and Obesity: The Impact of Visceral Fat — Diabetes Care* 2002; **25**: 2342-2349) — *Ann Intern Med* 2003; **138**:24-32)

ENJOY THE HOLIDAY SEASON



Orchid

Longwood Gardens, Kennett Square,
Pennsylvania, 2002



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WHAT IS THE BEST TEST TO ASSESS PAP TEST SPECIMEN ADEQUACY?

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- papilloma virus DNA within the previous 12 months;
- clinician inability to clearly visualize the cervix or sample the endocervical canal;
- immunosuppression;
- similar obscuring factor in consecutive Pap tests;
- insufficient previous screening (not participating in at least a biennial Pap test screening); and
- a postpartum repeat preferred for pregnant patients.

Issue 3. *What is the recommended follow-up for women with an unsatisfactory Pap test?*

The preferred management for

most women with an unsatisfactory Pap test is a repeat Pap test within 2 to 4 months. If the unsatisfactory result is due to obscuring inflammation and an organism is identified, consider specific treatment prior to repeating the Pap test. If the Pap test is repeatedly unsatisfactory due to obscuring blood, inflammation or necrosis, additional clinical evaluation, such as colposcopy and/or biopsy as appropriate, is suggested.

The reader is referred to the cited articles for an in-depth discussion of the rationale for the recommendations. (*J Lower Gen Tract Dis* 1997; **1**:100-106 — *Am J Clin Pathol* 2002; **118**:714-718)

HERPES SIMPLEX ANTIBODY TESTING — WHY AND WHEN?

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serologic tests that can accurately differentiate between antibodies to HSV-1 and HSV-2. The recent publication, *Sexually Transmitted Diseases Treatment Guidelines 2002*, from the Centers for Disease Control and Prevention (CDC), cautions physicians to specify the serologic type-specific glycoprotein G (gG) assay when ordering the test(s).

Editor's Note: Quest Diagnostics offers the HerpeSelect® HSV-1 and HSV-2 gG-based IgG antibody assays, which are noted in the CDC publication.

Consider the following patients for HSV-1 and HSV-2 antibody testing:

- anyone with suspicious symptoms or history suggestive of atypical or undiagnosed HSV infection;
- anyone diagnosed clinically who does not believe the diagnosis;
- anyone requesting or getting an STD screen, or who is at risk for

human immunodeficiency virus (HIV) infection;

- anyone whose partner has a genital HSV infection; and
- pregnant women with an atypical or unrecognized genital HSV-2 infection, or who are at risk of acquiring an HSV-1 or HSV-2 infection.

Safe and effective suppressive therapy is available for genital HSV infection. Patients want and need to know their HSV antibody status. This knowledge allows them to live their lives and maintain relationships without fear and shame. The reader is referred to the cited articles for more detailed information. (www.medscape.com — *The Diagnosis and Management of Genital Herpes: The Silent Epidemic* symposium held at the Donald E. Stephens Convention Center, Rosemont Conference Center in Rosemont, Illinois on June 22, 2002 — *MMWR* 2002; **51**(RR-6):32-34)