



Saint Luke's Regional Laboratories Clinical Laboratory Letter



November 2006

Persistent Low Levels of hCG

Persistent low levels of human chorionic gonadotropin (hCG) pose an infrequent but serious challenge to clinicians and laboratories. A recent publication indicates that a number of patients with low hCG levels and no evidence of pregnancy or imaging evidence of tumor have been subjected to unnecessary surgery and/or chemotherapy for misdiagnosed malignancy. A set of guidelines has been recommended to properly manage patients with persistently low hCG levels.

Researchers at the USA hCG Reference Service recently published data on serum samples from 170 women with low levels of hCG persisting for three months or longer that were sent to the service for consultation. The hCG levels ranged from 6.1 – 900 mIU/ml with an average result of 102 ± 152 mIU/ml. Of the 170 patients in the study, 13 were found to have a malignancy and the remaining 157 patients had false positive hCG, quiescent gestational trophoblastic disease (GTD) or pituitary hCG:

Medical Condition	# Cases
False positive	71
Quiescent GTD	69
Pituitary hCG	17
Active malignancy	13
Total	170

One hundred and eight (69%) of the 157 patients without a malignancy underwent unnecessary therapy including surgery and/or chemotherapy before consultation with the Reference Service. Forty-seven of the 71 patients with false positive hCG received chemotherapy and 9 underwent surgery. Forty-one of the 69 patients with a quiescent GTD received chemotherapy and 9 underwent hysterectomy. Two of the 17 patients with pituitary hCG received chemotherapy. hCG levels were unaffected by treatment in these patients.

Based on these findings, the USA hCG Reference Service proposed guidelines for managing patients with persistent low levels of hCG (Gynecol Oncol. 2006 Aug;102(2):165-72).

1. Determine if the hCG is biologically real.
The following criteria are used to identify false positive results (J Reprod Med, 49: 423-432, 2004).
 - a. The finding of a >5-fold difference in serum hCG results or negative hCG results with an alternative laboratory serum hCG test (essential criterion).
 - b. The presence of hCG in serum and absence of detectable hCG or hCG-related molecule in a parallel urine sample (essential criterion).
 - c. The observation of false positive results in other tests for molecules not normally present in serum, such as urine β -core fragment (confirmatory criterion).
 - d. The finding that a heterophilic antibody-blocking agent prevented or limited false detection (confirmatory criterion).
2. Send serum samples to a specialty laboratory. If the measured hCG is real, the serum samples should be sent to a specialty laboratory to determine if active gestational trophoblastic neoplasm, placental site trophoblastic tumor or non-trophoblastic malignancy is present.
3. Determine if the hCG is of pituitary origin. If the patient is peri- or post-menopause, or has had an oophorectomy, then pituitary hCG is likely. In that case, the patient should take hormone replacement therapy or oral contraceptives. After 2-3 weeks, this should suppress hCG production if it is of pituitary origin.

Additional or alternative testing for persistent low hCG can be arranged through consultation with one of Saint Luke's Regional Laboratories' clinical pathologists.

MRSA in the ED

Methicillin-resistant *Staphylococcus aureus* (MRSA) refers to strains of *S. aureus* that are resistant to all beta-lactam antibiotics, such as nafcillin and cephalosporins. In the hospital setting, MRSA can be associated with severe infections including sepsis, osteomyelitis, wound and surgical infections, and endocarditis. In recent years, a strain of MRSA associated with community acquired infections (CA-MRSA) has also become prevalent. CA-MRSA most commonly produces skin and soft tissue infections, but has also caused necrotizing pneumonia.

Data has recently been published (NEJM 2006;355:666-74) from a study of MRSA prevalence in skin and soft tissue infections in emergency department (ED) patients. The study took place during the month of August 2004, and included ED's in 11 U.S. cities from New York to Los Angeles, including Kansas City. Enrollment included 422 adult ED patients that had infections classified as abscesses (81%), wound infections (11%) and purulent cellulitis (8%). Cultures were performed on all patients with susceptibility testing performed on all isolates of *S. aureus*.

MRSA was found to be the most common identifiable cause of skin and soft tissue infection in 10 of the 11 ED's in the study. The prevalence of MRSA in 10 of the ED's ranged from 39% (Minneapolis) to 74% (Kansas City), and averaged 59% overall. The only ED in which methicillin-sensitive *S. aureus* was more prevalent than MRSA was in New York (40% vs. 15%). The majority of the MRSA strains from the study were sent to the CDC for typing and 99% were found to be consistent with previously characterized CA-MRSA. The most common identifiable risk factors for MRSA infection included presence of an abscess, reported spider bite, close contact of someone with a similar infection, and use of any antibiotic within the past month. Spontaneous infections, defined as no apparent precipitating factor, were also commonly reported. Susceptibility testing of the MRSA isolates revealed that 100% were susceptible to trimethoprim-sulfamethoxazole, 95% to clindamycin, 92% to tetracycline, and 60% to quinolones. Also of note from this study, although 80% of the patients received empirical antibiotic therapy, only 43% were infected with a strain susceptible to the chosen antibiotic. It is suggested that clinicians should culture skin and soft tissue

infections, as well as consider modifying empiric antibiotic therapy to include MRSA coverage.

Elevated Factor XI Levels are Associated with Stroke

Factor XI is a component of the intrinsic pathway of coagulation. It plays two roles in promoting hemostasis - a procoagulant action by increasing formation of fibrin, and an antifibrinolytic action by promoting the activity of a fibrinolytic inhibitor. Factor XI deficiency results in a mild to moderate bleeding disorder. A recent study indicated that high levels of factor XI are associated with venous thrombosis (N Engl J Med 2000;342:696-701). The authors reported a two-fold increased risk of venous thrombosis in subjects whose factor XI was above the 90th percentile for the population (factor XI level greater than 120%).

The association of factor XI levels with arterial thrombosis has not been established. Two studies suggested an association between elevated factor XI levels and coronary artery disease. A recent retrospective study investigated a possible relationship between factor XI levels and stroke (Am J Clin Pathol 2006;126:411-415). The subjects, all younger than 55 years, included 65 patients with stroke, 13 with TIA, and 17 with venous thrombosis. Forty healthy control subjects were age and sex-matched to the patient population. Factor XI activity and C-reactive protein (CRP) levels were assayed. Factor XI activity in the reference group ranged from 57%-155%, with a 95th percentile value of 141%. In the 78 patients with stroke or TIA, factor XI ranged from 55%-675%, and 22% of the patients had values higher than the 95th percentile of the reference population. The 17 patients with venous thrombosis had factor XI levels ranging from 71% to 196%, and 18% of these patients had values higher than the reference population 95th percentile. From this data, the odds ratio for stroke or TIA in patients with factor XI activity higher than the 95th percentile of the reference population is 5.3; for venous thrombosis this odds ratio is 4.1. There was no correlation between factor XI and CRP values, indicating that factor XI is not an acute phase reactant.

In summary, there is evidence that elevated factor XI activity is associated with both venous thrombosis and cerebrovascular disease. Further studies are warranted to determine whether this finding may be utilized to identify at-risk populations.

