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Gestational Diabetes Again

The December 2011 issue of the Clinical Laboratory Letter discussed the simplified one-step approach to diagnosis of gestational diabetes mellitus (GDM) that has been recommended by the International Association of Diabetes in Pregnancy Study Group (Diabetes Care 2011;34:s11). Since that time, the Committee on Obstetric Practice of the American College of Obstetricians and Gynecologists has advised their members not to follow the international guideline because it would lead to a significant increase in the prevalence of GDM and a significant increase in health care costs (Obstet Gynecol 2011;118:1379-93). ACOG recommends that all pregnant women should be screened for GDM by patient history, clinical risk factors, or a 50 gram one hour loading test. Diagnosis should be confirmed by the 100 gram three hour oral glucose tolerance test.

According to ACOG, either the plasma glucose cutoffs established by Carpenter and Coustan (C&C) or the National Diabetes Data Group (NDDG) can be used for interpretation.

Sample	C&C (mg/dL)	NDDG (mg/dL)
Fasting	95	105
1 Hour	180	190
2 Hours	155	165
3 Hours	140	145

Physicians need to be aware that two sets of guidelines for GDM screening have been issued that have different testing strategies, interpretive criteria and sensitivities.

Testing Inpatients for Hypercoagulability

A panel of tests for hypercoagulability is often ordered for inpatients with deep vein thrombosis, pulmonary embolism or arterial thrombosis. However, the value of this testing during hospitalization is questionable for the following reasons.

Acute thrombosis transiently decreases protein C, protein S and antithrombin. Factor VIII and fibrinogen often increase, because they are acute phase reactants. Heparin therapy can lower antithrombin levels and impair interpretation of clot-based assays for lupus anticoagulants and proteins C and S if the level of heparin is above the therapeutic range. Warfarin therapy decreases protein C and protein S levels because they are vitamin K dependent proteins. If a low value is obtained for any of these proteins during an acute event, testing must be repeated once the patient has fully recovered and is off of anticoagulants.

Genetic testing for Factor V Leiden and prothrombin gene mutations is not affected by medical acuity or anticoagulants, but the activated protein C resistance test, which is a screening test for Factor V Leiden, is decreased by acute thrombosis. This information is not needed for immediate clinical management.

The optimal time to order thrombophilia testing is when a patient is asymptomatic and no longer on anticoagulant therapy. In general, testing should be performed 4 to 6 weeks after discontinuing warfarin, direct thrombin inhibitors or fibrinolytic agents. This time interval is also necessary to allow acute-phase reactant proteins to return to baseline.

For these reasons, Saint Luke's Regional Laboratories recommends that hypercoaguable tests should **not** be ordered during hospitalization. Rather, testing should be performed in the outpatient setting after the patient has stabilized and is off of anticoagulant therapy.

An Easier Way to Investigate Prolonged Protimes or PTTs

The Prothrombin Time (Protime, PT) assesses the coagulation factors of the extrinsic and common pathways. The PT may be prolonged by deficiency of a single or multiple coagulation factors (Factor VII, Factor X, Factor V, Factor II or fibrinogen). The most common cause of a prolonged PT is warfarin therapy. Less commonly, PT may be prolonged due

to the presence of a specific coagulation factor inhibitor or the lupus anticoagulant.

The activated partial thromboplastin time (APTT) is a measure of the integrity of the intrinsic and common pathways of the coagulation cascade. Deficiencies or inhibitors of coagulation factors XII, XI, X, IX, VIII, V, II, and fibrinogen can prolong the APTT. The most common causes of a prolonged APTT include heparin therapy or sample contamination, coagulation factor deficiency, lupus anticoagulant, or a specific coagulation factor inhibitor.

Much confusion exists regarding the appropriate coagulation tests to order and the interpretation of the results. In order to simplify this testing, Saint Luke's Regional Laboratories has introduced two simplified test orders. Physicians can now order either the **"Prolonged PT Workup"** or **"Prolonged PTT Workup"**. The laboratory will perform as much testing as necessary to determine the cause of the prolongation and issue an interpretive report.

Specimen requirement is two blue top and one red top tubes of blood.

Preoperative Assessment of Platelet Inhibition by Plavix

Preoperative management of patients who are taking Plavix and require an invasive procedure or surgery can be problematic. Operating on patients who are taking Plavix is associated with excessive bleeding, but discontinuing Plavix therapy prior to surgery has been associated with a 20% incidence of ischemic events.

At least 3 clinical practice guidelines provide direction regarding the timing of surgery in patients receiving Plavix. Each of these guidelines recommends discontinuing Plavix for at least 3 to 7 days prior to surgery to allow platelet function to return to normal and decrease the risk of bleeding.

The American College of Chest Physicians Evidence Based Clinical Practice Guidelines from 2008 state that platelet function returns to normal 7 days after the last dose of clopidogrel (Chest 2008;133:71S-105S, specifically page 217S)

The Society of Thoracic Surgeons Clinical Practice Guidelines, which were updated in 2011, state that previous reports recommended a 5 to 7 day delay

after discontinuation of clopidogrel in patients requiring coronary artery bypass graft surgery to lessen bleeding (Ann Thorac Surg 2011;91:944-82, specifically page 951).

In between these two sets of guidelines is an update from May 2011 by the American College of Cardiology Foundation/American Heart Association for management of patients with unstable angina/non-ST elevation myocardial infarction. This document recommended withdrawing clopidogrel for at least 5 days prior to coronary artery bypass graft surgery (JACC 2011;57:1920-59).

All of these recommendations are based on the pharmacokinetics of clopidogrel. Inhibition of platelet aggregation can usually be detected 2 hours after a 300–600 mg loading dose of clopidogrel. Peak effect is usually evident at 6 hours after treatment. Clopidogrel irreversibly inhibits platelet function by blocking the binding of ADP to the platelet P2Y₁₂ receptor. Platelets blocked by clopidogrel are affected for the remainder of their lifespan, which is 7-10 days.

These recommendations do not take into account individualized response to drugs. Approximately 40% of patients have suboptimal antiplatelet response to clopidogrel. Patients who are hyporesponders or nonresponders would be expected to normalize platelet function even sooner than 5 to 7 days after discontinuing clopidogrel. An individual's response to clopidogrel can only be determined by performing platelet function testing. Saint Luke's Regional Laboratories offers the VerifyNow test. This test has been named the P2Y₁₂ Response Assay to avoid confusion with other tests such as the platelet function assay (PFA-100) and platelet aggregation.

Determination of the percent of platelet inhibition can be used preoperatively to determine if a patient who has been taking Plavix is at increased risk of bleeding. Values between 0 -20% are associated with minimal bleeding risk. More than 50% of patients achieve this level of inhibition within 3 days after discontinuing clopidogrel. Testing may reduce unnecessary surgical delays.

Specimen collection requirements were previously discussed in the January 2009 issue of the Clinical Laboratory Letter.