Human chorionic gonadotropin (hCG) is a commonly ordered test to determine pregnancy. It may also be ordered for several other, less common, reasons. The following discussion describes hCG and its diagnostic usefulness.

Approximately 1 week after fertilization the syncytiotrophoblast, or outer layer of cells of the placenta, begins producing the hormone human chorionic gonadotropin (hCG), which stimulates production of progesterone and estrogen to help maintain function of the corpus luteum. Serum hCG concentrations double approximately every 2 to 3 days during the first six weeks of pregnancy, then increase at a slower rate to reach peak concentrations of 20,000 to 200,000 mIU/mL at approximately 9 to 10 weeks' gestation. HCG levels then gradually decline and plateau during the second and third trimesters. HCG is excreted in the urine in concentrations comparable to those in blood. This rapid early production of hCG explains its primary use, the early detection and diagnosis of pregnancy. Structurally hCG consists of two non-covalently linked peptide subunits, alpha and beta, each having carbohydrate side chains. The alpha subunit is identical to the alpha subunit of the pituitary hormones follicle stimulating hormone (FSH), luteinizing hormone (LH), and thyroid stimulating hormone (TSH). The beta subunit is sufficiently different from the beta subunit of these hormones to allow development of antibodies which show essentially no cross-reactivity to the pituitary hormones. Today, immunoassays for hCG generally are specific for the beta subunit or for the intact hCG molecule.

Immunoassays for the qualitative (presence or absence) detection of hCG in urine are utilized as pregnancy tests, including home use tests. The sensitivity of these assays varies but a typical sensitivity is 25 mIU/mL. An assay with this sensitivity may diagnose pregnancy as early as 3 to 4 days after implantation, with positive results in 98% of women by the time of missed menses, which is approximately 7 days after implantation. Variability in results of qualitative urinary hCG assays may be due to the relative dilution of the urine sample (the concentrated first morning specimen should be used) or use of the test too early following conception. In addition, for home use kits false results may be due to misinterpretation or failure to follow instructions.

Although package inserts for all quantitative (numerical) serum hCG assays in the United States contain a warning that they are approved by the Food and Drug Administration only for normal pregnancy testing applications, these tests are routinely used for several other purposes. During the first six weeks of pregnancy, serum hCG concentrations rise linearly with a doubling time of 1.3 to 2 days, thus, a serum hCG level may be used to monitor suspected problem pregnancies. If levels decrease or rise less than 50% in 48 hours, the pregnancy is not normal and is most likely a failing pregnancy with an increased risk of spontaneous abortion or is potentially an ectopic pregnancy in which the fertilized ovum is implanted in a site other than the uterus. Typically in ectopic pregnancies the hCG levels plateau or have a slower rate of decline than is seen with impending spontaneous abortions, but this is not always true. Another use of hCG levels is in the monitoring and management of the pregnancy of patients suffering hyperemesis gravidarum, which is severe nausea and vomiting that can be fatal if not treated. Occasionally hCG levels may be used in the detection of multiple pregnancies because higher levels are seen with multiple fetuses.

The triple analyte screen for the detection of Down syndrome during the second trimester includes determination of maternal serum unconjugated estriol and alpha fetoprotein (AFP) as well as hCG. The combination of higher than normal hCG levels (gestational age dependent) and lower unconjugated estriol and AFP is associated with an increased risk of Down syndrome. Use of a fourth maternal serum test, inhibin, in combination with the triple screen has been shown to increase the predictive ability of the markers. Recently, a test for a variant form of hCG, hyperglycosylated human chorionic gonadotropin (H-hCG), also known as Invasive Trophoblast Antigen (ITA), in urine has been shown to be useful in screening for Down syndrome in the first trimester of pregnancy.

Another widespread use of quantitative hCG levels is for the diagnosis and management of hCG-producing conditions and/or tumors, including various trophoblastic diseases, and testicular and germ cell neoplasms. hCG is a vital test in the identification of choriocarcinoma and is used in the management of treatment and in detecting recurrences of disease. HCG levels are essential for demonstrating the complete removal of hydatidiform mole tissue and for rapid identification of post molar tumor or persistent trophoblastic disease.

Laboratorians should be aware of the possible problems associated with any immunoassay and, in particular, with hCG immunoassays. There are currently more than 50 quantitative serum hCG immunoassays available in the United States and their specificity varies. The ability to detect hCG breakdown products or glycosylated variants can lead to different results when using different manufacturers’ assays. Variants or products such as nicked hCG, hyperglycosylated hCG, hCG minus C-terminal peptide, asialo hCG, and free beta subunit are more abundant or unique to trophoblastic
diseases. Thus, the specificity of the assay to these compounds is critical when assaying samples from patients with these diseases.

Another problem with quantitative hCG immunoassays was highly publicized in June 2001 when a woman was awarded $16.8 million because “false-positive” hCG results led to an incorrect diagnosis of cancer and unnecessary chemotherapy and surgery. Based on persistently elevated hCG levels in the absence of any other signs of pregnancy, the patient was diagnosed with trophoblastic choriocarcinoma, a very aggressive tumor. After chemotherapy failed to lower the hCG levels two successive surgeries were performed, but no trace of tumor was found in the uterine and lung tissue removed during surgery. During this time the elevated hCG results on 45 different samples from this patient were confirmed by two reference laboratories. It was later learned that all three laboratories used the same assay. Analysis by a fourth laboratory utilizing an in-house immunoassay determined that the hCG levels were normal. The false-positive results were caused by the presence of human anti-animal antibodies or heterophilic antibodies, which can interfere with any immunoassays. Because of the awareness raised by this case, laboratorians should be proactive when investigating elevated hCG results that can lead to surgery or chemotherapy. At a minimum, one should be familiar with the specificity of the immunoassay that they use. Results should be double-checked using a serum assay from a different manufacturer or a urine-based assay system. Samples for which diluted and undiluted results are very different should also be further investigated.

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