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Human Chorionic Gonadotropin

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Introduction

Human chorionic gonadotropin (hCG) is a chemical created by trophoblast tissue, tissue typically found in early embryos and which will eventually be part of the placenta. Measuring hCG levels can be helpful in identifying a normal pregnancy, pathologic pregnancy, and can also be useful following an aborted pregnancy. There is also a benefit in measuring hCG in a variety of cancers including choriocarcinoma and extra-uterine malignancies.

Etiology and Epidemiology

Human chorionic gonadotropin is a hormone produced primarily by syncytiotrophoblastic cells of the placenta during pregnancy. The hormone stimulates the corpus luteum to produce progesterone to maintain the pregnancy. Smaller amounts of hCG are also produced in the pituitary gland, the liver, and the colon.[1] As previously mentioned, certain malignancies can also produce either hCG or hCG-related hormone. Trophoblastic cancers (hydatidiform mole, choriocarcinoma, and germ cell tumors) are associated with high serum levels of hCG-related molecules.

The hormone itself is a glycoprotein composed of two subunits, the alpha and beta subunits.[1] There are multiple forms found in the serum and urine during pregnancy including the intact hormone and each of the free subunits. HCG is primarily catabolized by the liver, although about 20% is excreted in the urine. The beta subunit is degraded in the kidney to make a core fragment which is measured by urine hCG tests.

Specimen Requirements and Procedure

Urine Testing

- Urine should not be collected after the patient has been drinking a large amount of fluid, as a dilute specimen may result in a falsely negative test.[2]
- Blood in the urine may cause a false positive test result.

Serum Testing

- Peripheral blood can be obtained for a serum hCG test.

Diagnostic Tests

Serum tests for hCG are immunometric assays. This means that they use 2two antibodies that bind to the hCG molecule, a fixed antibody and a radiolabeled antibody which adhere to different sites on the molecule, sandwiching and immobilize the molecule to make it detectable.[3] Assays involve washing away the excess serum components and measuring the amount of remaining

labeled hCG to give a quantitative result. There are more than 100 different assays commercially available which results in significant variability in reported values.

Urine assays are similar, although many detect total hCG levels greater than 20 mIU/mL. [4] Many over-the-counter urine pregnancy tests do not detect hyperglycosylated hCG, which accounts for most of the hCG in early pregnancy, resulting in a wide range of sensitivities of these tests.

Serum testing is much more sensitive and specific than urine testing. Urine testing, however, is more convenient, affordable, comfortable for patients, has a fast turnaround (5 to 10 minutes), and does not require a medical prescription.

Testing Procedures

Urine Testing

- Urine is placed in or on a designated receptacle (most commercially available and medical point of care tests)
- An indicator (typically a colored line or symbol), along with a control, will appear if the test is positive
- An isolated control line/symbol will be evident if the test is negative

Serum Testing

- Serum hCG testing is performed in a laboratory equipped with the proper machinery and uses a peripheral blood sample
- If a hook effect/gestational trophoblastic disease is suspected, the lab should perform a dilution prior to testing

Interfering Factors

There are multiple reasons why an hCG test (serum or urine) may have a false report. While uncommon, false positive hCG tests can result in unnecessary medical care and/or irreversible surgical procedures. False negatives may be equally concerning and result in a delay in care or diagnostic evaluation. Potential causes of false results are listed and briefly discussed.

Serum False Positives (1/1000 to 1/10,000) [5]

- Ectopic production of hCG (hydatidiform mole, choriocarcinoma, and germ cell tumors, [6], in addition to multiple myeloma, stomach, liver, lung, bladder, pancreatic, breast, colon, cervical, and endometrial cancers)[7][8][9][10][11]
- Heterophile antibodies (autoantibodies and antibodies formed after exposure to animal products that interact with the assay antibodies)[12][13]
- Rheumatoid factors (can bind the antibodies in the assay as well)
- IgA deficiency[14]
- Chronic renal failure or ESRD on hemodialysis (rare)[15]
- Red blood cell or plasma transfusion of blood with hCG in it have been reported

- Exogenous hCG preparations for weight loss, assisted reproduction, doping[16]

Serum False Negatives

- Early measurement after conception
- "Hook effect" can occur when hCG levels are about 500,000 mIU/mL.[17] This is because there are so many hCG molecules that they saturate both the tracer and the antibodies separately, which doesn't allow for the sandwiching of the tracer-hCG-antibody required for the measurement. This means that all of the complexes are washed away, giving a false-negative result. If gestational trophoblastic disease is suspected, the lab should perform a dilution prior to testing.

Urine False Positives

- Blood or protein in the urine
- Human error in result interpretation
- Ectopic production of hCG
- Exogenous hCG
- Drugs (aspirin, carbamazepine, methadone, high urinary pH and seminal fluid)[18]

Urine False Negatives

- Early measurement after conception
- Dilute urine specimen[2]
- "Hook effect" as discussed above

Results, Reporting, and Critical Findings

HCG levels are reported in milli-international units of hCG hormone per milliliter of blood, or mIU/mL. International unit per liter (IU/L) may also be used.

Urine hCG testing is qualitative, reporting a positive or negative result. The assays detect hCG levels typically starting at 20 to 50 (reportedly as low as 6.3 to 12.5)[19] mIU/mL, corresponding to levels at approximately 4 weeks post-conception.

Serum assays can measure beta-hCG as low as 1 to 2 mIU/mL.

Clinical Significance

Pregnancy

HCG is an important hormone in pregnancy, and its clinical utility is primarily centered around its detection in early pregnancy, along with serial measurement during pregnancy and pregnancy-related complications.

Levels of hCG can vary widely between women with normal pregnancies. Typically, serum and urine concentrations of hCG rise exponentially in the first trimester of pregnancy, doubling about every 24 hours during the first 8 weeks. The peak is usually around 10 weeks of gestation and

then levels decrease until about the 16th week of gestation where they remain fairly constant until term.[3]

Patients who have hCG levels that plateau prior to 8 weeks or that fail to double commonly have a nonviable pregnancy, whether intra-uterine or extra-uterine. Extra-uterine (ectopic) pregnancies usually have a rate-of-rise that is low without the typical doubling. However, given the large range of normal hCG levels and inconsistent rates-of-rise of this hormone, checking serum levels is typically paired with ultrasound evaluation to improve sensitivity and specificity.[20]

Return of hCG to zero following delivery or termination of pregnancy ranges from 7 to 60 days.[21] Trending the fall of hCG levels can be important in termination of molar pregnancies and also following the termination of normal or ectopic pregnancies to be assured that the therapy has been successful.

It notable that there are many different combinations of antibodies used in commercial assays. This results in heterogeneous results with as much as a 50-fold difference in immunoassay results.[3] This is clinically relevant, particularly when comparing results from different laboratories in different facilities/hospitals when examining low values following pregnancy termination or trophoblastic disease.

Gestational Trophoblastic Disease

Detection of hCG is also useful in the evaluation of trophoblastic disease, including complete and partial hydatidiform mole, postmolar tumor, gestational choriocarcinoma, testicular choriocarcinoma, and placental site trophoblastic disease. All of these entities produce hCG, varying levels of which are reported on commercial assays. A total hCG level of greater than 100,000 mIU/mL in early pregnancy, for example, is highly suggestive of a complete hydatidiform mole,[22] although many normal pregnancies may reach this level at their peak around weeks 8 to 11 of gestation. Precise hCG measurements are important to assess the tumor mass, the successful treatment of malignancy, and to test for recurrence or persistence of disease.[6]

Non-Pregnant Patients

HCG in the serum increases with age in nonpregnant women. A cut off of 14 mIU/mL has been suggested for use in interpreting results in women over the age of 55. In all nonpregnant patients, testicular cancer, ovarian cancer, bladder cancer, or other malignancy should be evaluated as a source of persistently positive hCG testing.

Enhancing Healthcare Team Outcomes

Knowing the utility and variability of different hCG assays is clinically relevant to a wide range of medical providers. False positive and false negative testing has a large impact on patient care. All providers in a patient care team should be aware of common limitations in testing, for example, urine assay false positives with hematuria, false negatives with dilute urine, along with more obscure but still very relevant causes of inaccurate testing. Interpreting results that may be false should be undergone with care to help prevent unnecessary testing and treatment.[23] (Level V) Collaboration, shared decision making, and communication are critical elements in good patient care.

Review Questions

- Access free multiple choice questions on this topic.
- Comment on this article.

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