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Avoiding inappropriate clinical decisions based on false-positive human chorionic gonadotropin test results. ACOG Committee Opinion No. 278. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2002;100:1057-9.

Avoiding Inappropriate Clinical Decisions Based on False-Positive Human Chorionic Gonadotropin Test Results

ABSTRACT: Clinically significant false-positive human chorionic gonadotropin (hCG) test results are rare. However, some individuals have circulating factors in their serum (eg, heterophilic antibodies or nonactive forms of hCG) that interact with the hCG antibody and cause unusual or unexpected test results. False-positive and false-negative test results can occur with any specimen, and caution should be exercised when clinical findings and laboratory results are discordant. Methods to rule out the presence of interfering substances include using a urine test, rerunning the assay with serial dilutions of serum, preabsorbing serum, and using another assay. Physicians must decide whether the risks of waiting for confirmation of results outweigh the risks of failing to take immediate medical action. Patients should be notified if they are at risk for recurrent false-positive hCG test results, and this information should be included in the patient's medical record.

Clinical management of many gynecologic conditions has improved dramatically over recent decades through the development of very sensitive and highly specific assays for hormones, particularly human chorionic gonadotropin (hCG). These assays have revolutionized the management of ectopic pregnancy and gestational trophoblastic disease, which now have a substantially lower mortality rate as a result of the ability to quantitate circulating (serum) and urinary hCG.

With the technologic improvements, hCG assays are now capable of detecting the presence of a pregnancy before a missed menstrual period. It is vital to remember that, despite technical advances, the ability of laboratory measurements to guide the clinician appropriately in every circumstance is limited (1–3). The purpose of this Committee Opinion is to offer recommendations to better manage situations in which hCG assays may provide false-positive results.

Some individuals have circulating factors in their serum that interact with the hCG antibody. The most common are heterophilic antibodies. These are human antibodies directed against animal-derived antigens used

in immunoassays (1, 4–9). Individuals who have worked as animal laboratory technicians or in veterinary facilities or who were reared on farms are more likely to develop heterophilic antibodies. Immunoassays of all kinds use animal antibodies. People with heterophilic antibodies might have unusual results in a number of different kinds of assays. However, because the animal antibodies are used in different amounts and with other reagents in each assay system, a person with heterophilic antibodies will not always have an unusual or unexpected result. Results can differ depending on the particular assay used.

Clinically significant false-positive results are rare. One report noted that 5 of 162 women studied had evidence of assay interference sufficient to provide misleading results (10). If results are misleading, they usually are seen with values below 1,000 mIU/mL. To rule out the presence of heterophilic antibodies or other interfering substances, several methods can be used:

- A urine test (either quantitative or qualitative) for hCG can be performed. Because heterophilic antibodies are not present in urine, if the urine test result is negative and the serum test result is persistently positive, interference in the serum immunoassay is confirmed if the serum value is ≥ 50 mIU/mL (3).
- The assay can be rerun with serial dilutions of the serum. Because heterophilic antibodies are directed to reagents in the immunoassay and not hCG, their interaction with the hCG curve will not be linear. Lack of linearity confirms assay interference.
- Some laboratories can preabsorb serum to remove heterophilic antibodies before performing the assay. If the result becomes negative after removal of the heterophilic antibody, interference can be confirmed (11).

There are other ways in which the amount of “true” hCG can be measured differently or even incorrectly by immunoassays. The size of the hCG molecule circulating in the blood of individuals may vary as a result of differences in the protein and carbohydrate structure of hCG. This type of variation is called *microheterogeneity* of hCG, and it sometimes can account for differences in measurements reported by different assays. Additionally, some individuals may produce aberrant forms of hCG that are not biologically active—or are other hormones

entirely—that will cross-react with the hCG assays. Still others may partly break down circulating hCG into nonbiologically active forms that react differently with the various assay systems. In these circumstances, substances other than native, biologically active hCG may be recognized by the assay system. Repeating the hCG measurement in a different assay system can best detect this problem.

Wide variations between repeat runs of the same assay could result from serum factors interfering with the assay. Serial dilution of the specimen will be helpful in documenting nonlinearity and confirming the presence of interference.

Finally, inherent assay factors can result in false-positive hCG results. Repeat testing using a different assay system may confirm that the result was falsely positive if the result is now negative.

Patients with evidence of hCG assay interference should be notified that they are at risk for recurrent false-positive hCG assay results. These patients should be instructed to inform all future health care practitioners of this problem, and the information should be included in the patient’s medical record.

In summary, modern assay methods have almost eliminated laboratory error. However, false-positive and false-negative test results can occur with any specimen. Caution should be exercised whenever clinical findings and laboratory results are discordant. Although false-positive serum hCG results are rare, if unrecognized, they may lead to unwarranted clinical interventions for conditions such as persistent trophoblastic disease. The physician must judge whether the risks of waiting for confirmation of results outweigh the risks of failing to take immediate action.

References

1. Cole LA, Kardana A. Discordant results in human chorionic gonadotropin assays. *Clin Chem* 1992;38:263–70.
2. Cole LA, Rinne KM, Shahabi S, Omrani A. False-positive hCG assay results leading to unnecessary surgery and chemotherapy and needless occurrences of diabetes and coma. *Clin Chem* 1999;45:313–4.
3. Rotmensch S, Cole LA. False diagnosis and needless therapy of presumed malignant disease in women with false-positive human chorionic gonadotropin concentrations. *Lancet* 2000;355:712–5.
4. Boscato LM, Stuart MC. Incidence and specificity of interference in two-site immunoassays. *Clin Chem* 1986; 32:1491–5.
5. Boscato LM, Stuart MC. Heterophilic antibodies: a problem for all immunoassays. *Clin Chem* 1988;34:27–33.

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6. Check JH, Nowroozi K, Chase JS, Lauer C, Elkins B, Wu CH. False-positive human chorionic gonadotropin levels caused by a heterophile antibody with the immunoradiometric assay. *Am J Obstet Gynecol* 1988;158:99–100.
 7. Weber TH, Kapyaho KI, Tanner P. Endogenous interference in immunoassays in clinical chemistry. A review. *Scand J Clin Lab Invest Suppl* 1990;201:77–82.
 8. Berglund L, Holmberg NG. Heterophilic antibodies against rabbit serum causing falsely elevated gonadotropin levels. *Acta Obstet Gynecol Scand* 1989;68:377–8.
 9. King IR, Doody MC. False-positive hCG by enzyme immunoassay resulting in repeated chemotherapy. *Obstet Gynecol* 1995;86:682–3.
 10. Rzasa PJ, Caride VJ, Prokop EK. Discordant inter-kit results in the radioimmunoassay for choriogonadotropin in serum. *Clin Chem* 1984;30:1240–3.
 11. Cole LA. Phantom hCG and phantom choriocarcinoma. *Gynecol Oncol* 1998;71:325–9.