Fewer false-positive pregnancy results with intact hCG

IN CANCER PATIENTS, 90 PERCENT OF FALSE-POSITIVES ELIMINATED

Anne Paxton

April 2018—When women of childbearing age check in at a cancer center where they might be undergoing medical or surgical treatment, the screening protocol is often to test them for pregnancy, primarily by quantifying serum β-hCG. But because a form of the β-hCG subunit can also be produced by several epithelial cancers, false-positive pregnancy results are more common in patients who have cancer.

With the use of a different test, most of those false-positives can be avoided, a new study conducted at Memorial Sloan Kettering Cancer Center suggests. The study, "Reducing False-Positive Pregnancy Test Results in Patients with Cancer," found that 90 percent of false-positives were eliminated when the samples were tested with intact human chorionic gonadotropin, says lead author Samuel I. McCash, MD, of the Department of Laboratory Medicine.

Dr. McCash

Dr. McCash, who directs the cancer center's Rockefeller Outpatient Pavilion laboratory in New York City, and his colleagues conclude that by using a reagent specific for intact hCG instead of β-hCG, laboratories can reduce the rate of false-positive pregnancy test results among patients with cancer while preserving screening sensitivity (McCash SI, et al. *Obstet Gynecol.* 2017;130[4]:825–829).

Memorial Sloan Kettering has a high proportion of false-positive pregnancy tests, Dr. McCash says. "We've found that a lot of different types of cancers can produce β-hCG, which is the marker used by almost all pregnancy tests." Intact hCG, on the other hand, can distinguish between pregnancy and cancer. Since intact hCG predominates in early pregnancy, the researchers tested whether the use of a reagent specific for intact hCG would reduce false-positives.

Reviewing 3,679 serum pregnancy screens from Oct. 21, 2014 to Jan. 20, 2015 and April 1, 2015 to June 2, 2015 on stored frozen specimens, the research team found 64 samples having total β-hCG values of 5 milli-international units/mL or greater. Assays of patients being monitored for trophoblastic cancer were excluded because the pregnancy test had been inappropriately ordered. Also excluded were repeat tests on the same patient.

The researchers tested the 64 samples on the Tosoh AIA 2000 automated immunoassay analyzer by immunoenzymometric assay, which measures both intact hCG and β-hCG with an immobilized capture antibody (magnetic bead) specific for the C-terminal peptide region of β-hCG. The capture antibody makes the assay specific for hCG as distinct from other similar proteins such as luteinizing hormone, FSH, and thyroid stimulating hormones.

Intact hCG will be positive only when intact hCG is present. "And intact hCG is actually more specific, especially in early pregnancy, at detecting pregnancy," Dr. McCash says. "β-hCG is lower in early pregnancy, making it more difficult to distinguish pregnancy versus mildly elevated β-hCG with some malignancies." Testing for the intact β-hCG is particularly helpful and specific in this setting, he adds.

“We thought if we brought in this test that looks at intact hCG only, it might be able to eliminate a large majority of false-positives. And that would have a huge impact on cases.” Since the researchers had access to the patient histories, “We knew whether those patients who tested positive on the β-hCG were pregnant or not, and from that we could tell that 90 percent of the false-positives could have been avoided if they had used the intact hCG.”

Intact hCG can come from a few places in the body, Dr. McCash explains. “One is from a fetus that’s growing in pregnancy, another is from trophoblastic cancer, and another is from the pituitary gland, which produces a very small amount of hCG.” When a person goes into menopause, he adds, changes in the hormone regulation in the body cause the pituitary to start producing elevated amounts of hCG, enough to make a qualitative pregnancy test turn positive when, in fact, the patient is not pregnant.

False-positives result when epithelial cancers produce a form of the β-hCG subunit. Among the 17 cancers that produced β-hCG in the patients studied were breast mixed ductal or lobular carcinoma, cervical squamous cell carcinoma, colonic adenocarcinoma, pancreatic adenocarcinoma, and thyroid medullary carcinoma.

By prompting incorrect therapy, false-positives can cause direct harm to the patient. “It is most distressing to patients when a pregnancy test unexpectedly comes back positive. It will hold everything up,” Dr. McCash notes. “The patient can’t get chemotherapy and can’t get any procedures, and we can’t do any of the imaging studies.” There is also the unnecessary worry about an unintended pregnancy during cancer therapy, the study authors note.

There is no technological reason why cancer centers have used the β-hCG assay rather than intact hCG, Dr. McCash says. “It’s more just what’s available in the U.S. The β-hCG assays were approved by the FDA for pregnancy testing, and it’s been easier to transfer to different instruments rather than having the FDA approve an intact version. So it’s very easy to market it and most people have gone with it. The intact hCG test has sort of slipped under the rug and gotten lost in the mix over time. The companies still have the reagent, but it’s more often used in Europe and Japan.”

One limitation of the study, Dr. McCash cautions, is that a larger cohort of pregnant patients would have to be tested with intact reagent to better characterize actual assay sensitivity and the false-negative rate. At MSK, patients without cancer were not available in the patient population. “Every study gets more powerful as you have more subjects to test,” he says. “We would need more negative patients, but it would take a large number of people to be tested to do that. In our case, it took half a year to get 64 patients to test. If I wanted to get, say, 100 individuals, it would take another year, and to get 500 individuals would take five years.”

Nevertheless, with this study, he says, “The statistics indicate there is a 95 percent certainty the findings are true.” He thinks the possibility is low that the intact hCG assay has decreased sensitivity, because the monoclonal antibodies in the reagent are designed to capture and label normal intact hCG, and this particular assay is already FDA approved for use in detecting pregnancy.

Dr. McCash believes the study findings will be relevant and can be applied to other cancer treatment centers. “They do a lot of chemo, a lot of imaging, and a lot of surgery, and these patients are at higher risk of cancers that could produce the β-hCG that could cause the false-positives.”

Laboratories should also be interested in this study, although they alone may not have the decision capabilities about which pregnancy tests to use, Dr. McCash notes. “The best way for labs to consider changing tests is to work with the clinicians to bring potential issues to their attention and get their feedback. That’s why we published in a clinical journal. It’s the clinicians who will need to support laboratory initiatives and confirm, ‘I’m worried about false-positives in my patient, and I need the lab to change this test for me.’”
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