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Point-of-Care and Over-the-Counter Qualitative Human Chorionic Gonadotropin (hCG) Devices Remain Susceptible to False-Negative Results Caused by Excess hCG β Core Fragment

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Guest:
Dr. Gronowski is Professor in the Department of Pathology and Immunology and the Department of Obstetrics and Gynecology at the Washington University School of Medicine in St. Louis.

Bob Barrett: This is the podcast from *Clinical Chemistry*. I am Bob Barrett.

For many taking a home pregnancy test can be upsetting, particularly if there is not complete confidence in the result. The November 2013 print issue of *Clinical Chemistry* published a paper from a group led by Dr. Ann Gronowski that reported false-negative results in point-of-care and over-the-counter qualitative hCG devices. That paper has also been available online since August 2013.

Dr. Gronowski is Professor in the Department of Pathology and Immunology and the Department of Obstetrics and Gynecology at the Washington University School of Medicine in St. Louis. She is our guest in this podcast.

Dr. Gronowski, this latest report is a follow-up to a study you published a few years ago. Can you summarize what that earlier study showed?

Dr. Ann Gronowski: Yeah, sure Bob! In 2009, we reported that high concentrations of one of the forms of the pregnancy hormone hCG, called the hCG beta-core fragment, can cause false-negative results in point-of-care pregnancy tests that we use in the hospital.

In that paper, we identified three patients that had false-negative hCG results on point-of-care tests and their tests actually became positive after the urine was diluted. Those patients also had much higher concentrations of hCG beta-core fragment than they did regular hCG.

So we were able to confirm that the beta-core fragment was causing the problem by taking a random hCG positive urine sample and by adding excess hCG beta-core fragment and showing that the positive band disappeared in a dose dependent manner. This effect has come to be known as the variant hook effect.

This was an important observation because the hCG beta-core fragment is actually the predominant form of hCG that's found in the urine after about five weeks of pregnancy. Therefore, this is potentially a big problem, and we don't know how often the urine from pregnant women contains enough of that hCG beta-core fragment to actually cause false-negative results. Our findings were reported to the FDA in 2009.

Bob Barrett: In your most recent paper you seemed to have taken this observation one step further and looked at the pregnancy test sold over-the-counter. Now, what did you find there?

Dr. Ann Gronowski: So we made several interesting observations in this paper. First, the over-the-counter home pregnancy devices are also subject to the variant hook effect, and that's pretty much just as we suspected.

But when my co-author, Rob Nerenz, performed these experiments, he used the hospital point-of-care devices as a control. And we were quite surprised to find that the hospital pregnancy devices were more affected by the hCG beta-core fragment than the home pregnancy devices. We didn't expect to find that.

And it's also clear that despite the fact that the variant hook effect was reported to the FDA in 2009, manufacturers have not changed their devices to avoid this problem.

Bob Barrett: Did you just look at one over-the-counter pregnancy test device?

Dr. Ann Gronowski: No, actually we started by examining six over-the-counter devices and we selected two that seemed to be the most affected by the variant hook effect, and then we compared those two devices to the hospital device that we had made our original observations in four years ago and to a hospital device that we thought performs best when compared to various other hospital pregnancy devices.

So, the two worst over-the-counter home devices outperformed what we feel is one of the best point-of-care hospital devices.

Bob Barrett: Has anything been done by IVD manufacturers to address the variant hook effect in pregnancy devices?

Dr. Ann Gronowski: Well, a couple of things. First, I have noticed that some, but not all, manufacturers have added a sentence to their already lengthy and wordy package inserts that says something along the lines of, later in pregnancy urine can contain more hCG fragments and therefore the device is most effective when used early in pregnancy. However,

those comments don't report that diluting the sample will give a positive result.

And in addition, I doubt that many physicians really read the package inserts from pregnancy devices that are used in their hospitals and their clinics.

The second thing that I have seen is that I know moving forward the FDA is requiring manufacturers to investigate the variant hook effect in all new hCG devices that are being brought to market. However, this does not alleviate the problem with the devices that are currently on the market.

Bob Barrett: And this seems like a real problem. What do you think needs to be done and who should be doing it?

Dr. Ann Gronowski: Well, in my opinion several things need to be done. Most immediately we need to educate physicians, nurses, and other healthcare professionals that this is a problem, and programs like this really help in that regard.

Second, manufacturers need to make the possibility of variant hook effect clearly visible in their package insert and state that when this is suspected in a sample that a simple dilution of that sample can yield a positive result if the patient is truly pregnant. And this is important for sites that don't have any alternative way of testing for pregnancy.

Third, I think that in centers where quantitative serum hCG testing is available, this should be the preferred pregnancy test. Serum testing is not subject to the variant hook effect because the hCG beta-core fragment is not present in serum, only urine, and the quantitative serum assays are much more analytically sensitive. In major medical centers quantitative HCG assays are rapidly available 24 hours a day and most patients are having blood drawn for other testing.

So I think that hospitals have kind of clung to the qualitative urine test as a carryover from the days when getting a quantitative serum took many hours.

And in fact, many hospitals in Europe and abroad have completely eliminated the use of qualitative hCG testing in their centers.

And then finally, our laboratory is working to better define what ratio of beta-core fragment is required to cause the variant hook effect, and we hope that this will help manufacturers to produce devices that avoid false-negative results and may even allow them to modify their existing product.

Bob Barrett: Dr. Ann Gronowski is Professor in the Department of Pathology and Immunology and the Department of Obstetrics and Gynecology at Washington University School of Medicine in St. Louis. Much of her research is focused on hCG. She has been our guest in this podcast from *Clinical Chemistry.*

I am Bob Barrett. Thanks for listening!